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THE INDICATIONS AND LIMITATIONS OF PROSTATIC SURGERY IN THE PRESENCE OF CARDIAC DISEASE

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Since patients having abnormalities of micturition resulting from disease of the prostate are usually beyond middle life, they will show a rather high incidence of cardiac disability. In some instances the cardiac and circulatory condition is one which will permit surgical intervention with safety; in others the only safe procedure is palliation of the urinary obstruction until such time as treatment of the cardiac dysfunction has restored circulatory balance.

Complete urinary retention creates a surgical emergency and its relief is a matter of immediate concern. The bladder must be drained of urine and means provided for keeping it empty. Once this has been done, subsequent operation on the obstructed vesical outlet becomes an elective procedure which may or may not be wise.

It is now generally agreed that patients having cardiac lesions often tolerate operation unexpectedly well. Indeed, the condition of the circulatory system usually improves immediately on relief of the obstructed bladder. The patient past middle life is not to be considered a poor operative risk for surgery of the prostate merely because of his years. For these reasons a proper evaluation of the factors involved when cardiac disease and urinary obstruction of prostatic origin coëxist, is very important.

In studying these problems, the following classification has been made largely as a matter of convenience in discussion, because the problems of diagnosis and treatment in each differ significantly.

Group 1. Urinary retention developing during or after an acute cardiac crisis.

GROUP 2. Cardiac disease appearing after acute urinary retention or efforts to relieve it.

GROUP 3. Myocardial insufficiency in the presence of chronic urinary retention.

GROUP 1. The term *cardiac crisis* is intended to include some severe cases of angina pectoris, coronary thrombosis, and acute cardiac decompensation. In all three conditions it is necessary to confine the patient to bed for some time and otherwise to curtail his activities to a large extent. The weakness which accompanies these conditions and the restriction of fluid intake regarded as advantageous in treatment may be contributory factors to urinary retention. Chronic passive congestion resulting in oliguria and local edema of the pelvic viscera may also predispose to it. Besides this, urinary obstruction may appear as the result of vigorous diuretics, such as mercupurin. These may cause rapid excretion of 5 or 6 liters which makes such demands on the partially obstructed outlet of the bladder that complete retention supervenes. Or intravesical hemorrhage may occur spontaneously from the enlarged prostate and thus precipitate retention. Furthermore, the excessive use of morphia, amyl nitrite, or barbiturates tends to diminish the desire to urinate until a point is reached at which the detrusor becomes overstretched and temporarily loses adequate power to expel the contents of the bladder. Care must be taken to differentiate oliguria and true vesical retention of urine in order to avoid unnecessary catheterization.

The following 3 cases are discussed to illustrate the problems of diagnosis and treatment presented by this group of patients.

CASE 1. A merchant, aged 68, was admitted to hospital on account of cardiac decompensation and acute urinary retention. On 2 occasions during the preceding 18 months he had been treated for the same difficulties. He had been discharged from the hospital only 5 weeks earlier, after treatment for infarction of the myocardium, cardiac decompensation with pleural effusion, and urinary retention due to benign hyperplasia of the prostate. Treatment had consisted of digitalization, thoracentesis, diuresis by mercupurin and intermittent catheterization. After the acute cardiac insufficiency had been controlled and a satisfactory diuresis obtained, the patient was able to be out of bed. The blood pressure then measured 100/70 mm. Hg. Ability to empty the bladder returned gradually. After 4 weeks at home, cardiac failure recurred; and 5 days later, acute urinary retention. Constant urethral drainage at home was not tolerated, and he returned to the hospital. Thoracentesis was performed on the 1st, 10th, and 14th days in the hospital, 800 cc., 1000 cc., and 1200 cc. being removed on the respective occasions. Urethral catheterization and irrigation of the bladder was necessary three times daily. Mercupurin 1 cc. was administered intravenously on 3 occasions resulting in a urinary output of 2600 to 4400 cc. Digitalis folia 0.1 gm. was given daily. After 5 days, the patient could void spontaneously but carried a residual urine of 300 cc. For the first 10 days there was a daily rise in temperature to 101.5° but it was normal thereafter. On the 23rd day a transurethral prostatectomy was carried out under a low spinal anesthesia. Operation was performed with the patient in a semireclining position. The pulse remained at a rate of

80 per minute, respirations 22 per minute and the blood pressure measured 90/70 mm. Hg throughout the procedure. The bladder was drained by an inlying urethral catheter for 48 hours, after which the patient was able to empty it with ease. He was discharged 1 week later. At examination a month after discharge, there had been no recurrence of cardiac insufficiency or further urinary difficulty.

Here we have an example of recurrent cardiac decompensation, each episode being accompanied by progressively more severe urinary retention. From the first it was known that he had definite hyperplasia of the prostate. However, surgery was unnecessary since micturition became normal again after regaining compensation sufficiently for the patient to be allowed out of bed. At the second episode of decompensation, however, retention lasted longer and was more difficult to combat. At the third, prostatectomy or provision for permanent drainage was indicated.

The next case represents a somewhat different and less difficult problem than the foregoing, but is appropriately classed in the same group.

CASE 2. A clergyman, aged 63, was admitted 2 weeks after an acute attack of substernal pain which had lasted for 3 days. He had been ordered to bed by his local physician, but in spite of this he continued to have intermittent attacks of anginal pain. Gradually difficulty in voiding began, ending in total retention of urine necessitating catheterization. At the time of hospitalization there was no evidence of congestive failure and no evidence of cardiac abnormality was demonstrable by physical examination while the patient was at rest. The pulse was regular, 80 per minute, and the respiratory rate, 20. The blood pressure was 120/80 mm. Hg. A diagnosis of recent anterior myocardial infarction was made by aid of the electrocardiogram. The bladder could be palpated at the level of the umbilicus. The prostate was felt to be moderately enlarged on rectal examination. Upon catheterization, 1500 cc. of clear urine was obtained. Catheterization was carried out twice daily and the bladder irrigated. The non-protein nitrogen of the blood measured 35 mg.%. On the fourth day in the hospital, intravenous urograms showed prompt excretion of the opaque material from each kidney; the outlines of the renal pelves were normal. The fluid intake was increased to 3000 cc. and the amount of urine voided increased from 500 cc. to as much as 2000 cc. in 24 hours with the aid of diuretics. However, even after being out of bed for a week there was still a residual urine of 1100 cc. on occasions. On the 8th day in the hospital, 3 weeks after his attack of coronary occlusion, cystoscopic examination was performed and obstruction of the vesical outlet by an enlarged median lobe of the prostate and moderate lateral lobe hyperplasia was seen. The next day transurethral resection of the prostate was done under low spinal anesthesia. The blood pressure remained stable at 110/80 mm. Hg during operation. The urethral catheter was removed on the 4th day after operation and the patient was able to empty his bladder completely thereafter. He was discharged from the hospital 1 week later, and has continued well 2 months after operation.

This patient presents an instance of urinary retention occurring as a complication of coronary thrombosis without myocardial insufficiency of a degree severe enough to cause acute passive congestion. Digitalization was not necessary. The patient was found

to have also vesical atonia and benign hyperplasia of the prostate, the combination of which was sufficient to produce total retention. Subsequently with improvement in his general condition he was able to empty his bladder incompletely and continued to have a large residual urine. At cystoscopic examination it was seen that the inability to void was largely due to prostatic obstruction and not to a paralysis of the bladder. Renal function was normal and no significant infection was present. It was not necessary to drain the bladder suprapubically since catheterization was well tolerated. As this patient did not suffer from orthopnea, perineal prostatectomy could have been carried out but was deemed unnecessary. Following transurethral prostatectomy 3 weeks after the coronary thrombosis no further urinary difficulty was experienced.

The next case represents still another variation in clinical course, yet it falls into the same group as the above two.

CASE 3. A man, aged 80, was admitted to the hospital on account of inability to urinate for 3 days. For 10 years he had been treated intermittently in the Out-Patient Department for hypertensive heart disease with auricular fibrillation. There had been repeated episodes of difficult micturition; and after an attack of acute urinary retention 5 years before, prostatectomy was advised but was refused. At the present admission he was dyspneic, and scattered râles were heard at the base of the lungs. The heart was enlarged to the left and its action irregular. The blood pressure was 180/110 mm. Hg. The electrocardiogram showed auricular fibrillation and an abnormal ventricular complex. The bladder was palpable halfway to the umbilicus and at cystoscopic examination benign hyperplasia of the prostate causing total retention of urine was demonstrated. Urinalysis showed a specific gravity of 1.030, very slight trace of albumin, and 5 to 10 erythrocytes in the sediment. Digitalization was instituted and the bladder placed on constant drainage by a urethral catheter. The latter was poorly tolerated and 3 days later suprapubic cystotomy was performed. Phenolsulphonephthalein excretion was 45% the first hour and 15% the second hour. The blood urea nitrogen was measured at 31 mg. per 100 cc. The specific gravity of the urine varied from 1.008 to 1.030. In spite of digitalization and a well-established renal equilibrium after 3 weeks in the hospital the cardiac condition seemed too poor to permit prostatectomy. He was discharged from the hospital to recuperate at home while suprapubic drainage of the bladder was still being maintained. After 7 months at home, the catheter was removed. The urinary fistula healed quickly and normal micturition was resumed. There was no recurrence of urinary difficulty and he died 5 years later of bronchopneumonia. At postmortem examination, the important findings in addition to pneumonia were coronary sclerosis, cardiac hypertrophy and dilatation, benign hyperplasia of the prostate without urinary retention and a small papillary carcinoma of the rectum without metastasis.

This patient's course is described particularly to illustrate the value of conservative therapy when a serious contraindication to operation is present. The resumption of nearly normal micturition without prostatectomy is not rare in such cases. One must assume that this occurred as a result of coincident improvement of his cardiac condition, with relief of local edema and congestion of the

vesical outlet following drainage. Thus it is possible that a more accurate evaluation of every patient may permit avoiding operation for some. It is often possible to introduce the suprapubic catheter by the use of a trocar instead of subjecting the patient to the more extensive operative wound of a cystotomy.[1] This is a simple, safe procedure in a patient having a distended bladder. After improvement has taken place following drainage, the vesicle function can be tested by intermittent clamping of the suprapublic tube and allowing the patient to attempt micturition. This method of testing the patient's ability to empty the bladder is of value, particularly in those who are poor operative risks.

GROUP 2. In this group the urinary retention precedes the earliest abnormal cardiac manifestation. Many of the unexpected cardiac complications of prostatic surgery can be anticipated and possibly some prevented by a more searching investigation and longer preoperative preparation in individual instances. It is usually possible to estimate accurately the efficiency of the heart and its response to effort. This is of particular importance in elderly patients. Levine[3] has pointed out that in estimating the risk which a given cardiac condition adds to that of the contemplated operation, there are two important factors to be considered. The first and most important is the ability of the heart to respond to effort. If the cardiac condition has been well compensated and the patient able to lead an active life, the heart has already given evidence of being able to withstand a greater load than any operation will demand. It must be remembered also that the peripheral circulation may fail with equal facility whether the heart is diseased or not. Thus, the history of cardiac efficiency is even more important than the physical examination; whereas a history of breathlessness or substernal pain may designate the presence of cardiac disease even though physical examination is not remarkable. Such symptoms are more informing than the presence of a murmur or of cardiac hypertrophy.

The second important factor is the liability of the heart to the so-called "accidents" of heart disease. These unpredictable complications which may suddenly change the prognosis are acute coronary thrombosis, embolism, Adams-Stokes attacks, paroxysmal tachycardia, auricular fibrillation, bacterial endocarditis, and ventricular fibrillation. Fortunately, such postoperative complications are not common. Though it is impossible to foretell events in individual instances, one can classify all cases into those that are more and those that are less likely to develop these complications. Since prostatectomy is never an emergency operation, in this field of surgery particularly, it is possible and important to delay intervention in those patients who are more likely to develop one of the accidents of cardiac disease. This period of delay is not one of temporizing, but rather one of active therapy. The most important

feature is that of vesical drainage which permits return of maximal renal function, stabilization of peripheral circulation, and increase of cardiac efficiency. The patient's exercise tolerance is carefully studied and his activities steadily increased as it improves. Vital capacity studies are helpful in judging improvement of cardiac efficiency. The day-to-day chart of the pulse, respiration, blood pressure and fluid exchange, show at a glance the degree of improvement.

The following case is illustrative of the important features mentioned above.

CASE 4. A clerk, aged 57, had his first attack of urinary retention while on a long motor trip. He stopped twice a day for 3 days to be catheterized by physicians along the way. On the 4th day of his illness he was admitted to hospital. The past history revealed that he had had nocturia 2 to 3 times each night for several years and progressive increase of urinary frequency during the past year with associated loss in force and caliber of the urinary stream. Otherwise his general condition had been good and any abnormal cardio-respiratory symptoms were specifically denied. The heart sounds were rather distant and regular at a rate of 70. The blood pressure was 150/80 mm. Hg. The lungs were clear. The liver was not palpable. The bladder was palpable at the level of the umbilicus. By rectal examination the prostate was found to be symmetrically enlarged, smooth and firm. At cystoscopic examination, hyperplasia of all lobes of the prostate was found causing total retention of urine. Culture of the urine yielded a growth of enterococci. The urine contained a slight trace of albumin and the sediment showed 10 leukocytes per high-power field. A catheter was inserted into the distended bladder via a trocar passed just above the pubis. The patient was kept on constant drainage for 10 days, being encouraged meanwhile to be active about the ward. Though the blood urea nitrogen was normal, the phenolsulphonephthalein excretion was only 10% in the first 20 minutes, and 50% in 2 hours. On the 10th day transurethral prostatectomy was performed under spinal anesthesia and the suprapubic drainage of the bladder continued as before.

Two days after operation the patient complained of pain in the right side of the chest where dullness on percussion and diminished breath sounds were found. A few hours later he had a chill following which a transitory pleuritic friction rub was heard. The right side of the chest was splinted by strapping for relief of the pain which morphia did not control. The next morning there was bloody sputum, the heart was enlarged, its action irregular, and many moist râles were heard in the lungs. A Roentgen-ray film of the chest showed a pleural effusion on the right, elevation of both diaphragms and cardiac dilatation. Rapid digitalization was instituted. An electrocardiogram showed auricular fibrillation with a ventricular rate of 150 per minute. The patient received 1.4 gm. of digitalis folia in the next 24 hours and the heart rate became regular at 50. Digitalis was discontinued after decompensation had rapidly cleared, but bloody sputum persisted for 2 weeks. Fortunately there was no renal or local operative complication; he was allowed up 13 days after operation and was discharged from the hospital 1 week later. Micturition was performed normally after removal of the suprapubic catheter on the 15th postoperative day. The patient was entirely well and returned to work a month later.

This patient had as postoperative complications pulmonary embolism, paroxysmal auricular fibrillation, cardiac dilatation and decom-

pensation. In reviewing his history after recovery he admitted having had several attacks of dyspnea, palpitation and substernal pain in the past. Being of an apprehensive nature he had preferred for the sake of his family to withhold this information. After his recovery, on physical examination the heart seemed quite normal and the electrocardiogram showed no abnormality. In retrospect it is only fair to say that the period of preoperative preparation should have been longer and the evaulation of his response to effort more searching. It seems that had an accurate history been given and digitalis used before operation, myocardial insufficiency might have been avoided. However, one cannot assume that this would have prevented the pulmonary embolus. The merits of the use of the suprapubic catheter are here demonstrated again in the face of severe circulatory complications, for any additional complications commonly caused by the indwelling urethral catheter might have been sufficient to alter the ultimate result.

GROUP 3. We consider here those patients having chronic urinary retention due to the enlarged prostate and secondary cardiac dilatation with myocardial insufficiency. In general, it may be said that so far as the cardiac disease goes, the prognosis here is better than in those who have had previous coronary disease. However, it is to be remembered that coronary thrombosis can occur in anyone having coronary artery sclerosis. The latter anatomic finding is common in the older age groups.

The patients of this group usually have severe renal damage so that the prognosis depends more upon the potential renal reserve than on any other single factor. Here we find necessary the most prolonged preoperative preparation, but as a result of this preparation, some of the most gratifying end results are obtained. It has been said[3,4,5] that all cardiacs withstand surgery surprisingly well except for those who have nephritis, congestive failure, or coronary artery disease. The patient suffering from prostatism often has pyelonephritis and in the presence of coincident heart disease the problem of treatment becomes increasingly difficult. But by proper preoperative care, and timing of the operation the risk is greatly diminished. The period of preparation if long, need not be spent in the hospital. It may be necessary to institute drainage for several months before surgical intervention is safe. One can be certain of the best possible prognosis for the individual patient if he withholds operation a little longer than seems really necessary. The following case is illustrative of the proper management of the problems presented by this group.

CASE 5. A retired business man, aged 71, was admitted to the hospital because of frequency, dribbling and incontinence of urine for 3 months. For 3 weeks the patient had noted progressive dyspnea, orthopnea, and swelling of the feet and legs. He was found to be dehydrated and emaciated. The tongue was coated. The heart was greatly enlarged to the left,

the apical impulse being in the midaxillary line in the 6th interspace. The blood pressure measured 170/90 mm. Hg. The breath sounds were diminished at both bases and numerous moist râles were heard over both lower lobes of the lungs. A presystolic murmur was heard at the apex. There was edema of the legs extending up to the knees. The bladder was palpable just below the umbilicus. The prostate was greatly enlarged and there was a hard nodule palpable in the right lobe. The patient was digitalized and the bladder drained by the suprapubic route. After 3 days edema of the legs had cleared, the apical impulse was found in the 5th interspace just outside the nipple line, but the râles persisted in the lungs. The diastolic murmur could no longer be heard. In spite of constant drainage of the bladder the non-protein nitrogen of the blood rose from 62 mg. % to 94 mg. per 100 cc. The systolic blood pressure fell gradually from a level of 170 to 130 mm. Hg and the diastolic from 90 to 60. During the next 2 months the patient gradually improved. The vital pulmonary capacity increased from 1700 to 3200 cc. All signs of cardiac decompensation completely disappeared. The non-protein nitrogen of the blood fell to a level of 40 mg. per 100 cc. but the phenolsulphonephthalein excretion did not exceed 35 per 100 cc. The electrocardiogram showed inversion of the T wave in all leads and an abnormal Lead IV. After 56 days of preparation a transurethral prostatectomy was performed. The tissue proved to be carcinoma of the prostate. Seven days later the suprapubic catheter was removed and normal micturition occurred thereafter. He was discharged from the hospital a week later, 70 days after admission. Three months later he returned because of lobar pneumonia; and died within 24 hours. Autopsy showed lobar pneumonia due to *B. Friedländeri* (*Klebsiella pneumoniæ*) involving the entire right lung, and a blood culture positive for the same organism. There was hypertrophy (440 gm.) and dilatation of the heart and an acute pericarditis. The coronary arteries showed only a slight degree of hyaline thickening of the intima and fibrosis of the media. The carcinoma of the prostate had begun to invade the periprostatic tissue but there were no demonstrable lymph node metastases. Roentgen therapy had caused no apparent inhibition of growth of neoplastic cells. The vesical orifice presented a "cup"-like depression in the prostatic portion with a resulting ample outlet. The mucosa over the prostatic urethra was well healed. There was a mild chronic cystitis. The kidneys appeared normal and microscopic examination showed a rather slight degree of pyelonephritis (quite inactive) which in view of the past history of marked urinary retention and infection as well as poor renal function, was striking.

Such patients will always require prolonged preoperative preparation. For these the simplest immediate solution is installation of a suprapubic catheter. After drainage has been established there often follows a short period when the patient seems to be worse. Complete disorientation is common and the non-protein nitrogen of the blood increases in amount. Also during this time there is usually a noticeable drop in blood pressure which must be explained by the sudden relief of obstruction and resumption of free excretion. The transitory rise in non-protein nitrogen of the blood and varying degrees of oliguria to anuria may be explained on the basis of previous dehydration and renal vascular engorgement caused by urinary obstruction. Under the conditions imposed by urinary retention, the kidney is forced to concentrate to the limits of its ability constantly. What happens to such a kidney when all obstruction is

released, depends on a reciprocal relationship with the entire cardiovascular system. In the case above described there was a quick response of the heart to digitalis and other general measures but the kidneys were very slow to respond to treatment. Only after almost 2 months of therapy was the patient considered in a condition suitable for operation. From this, recovery was prompt, but 3 months later death occurred from pneumonia. Postmortem examination of the heart and kidneys showed conditions far closer to normal than one would have expected considering his former critical state.

Analysis of 25 Cases of Prostatism Associated with Heart Disease. In order to gain a clearer conception of the indications for and limitations of prostatic surgery presented by patients having cardiac disease a study of the records of 25 such patients has been made. The salient features of these records is presented in Table 1. The only selection that has been used has been an effort to choose primarily patients who have been in this hospital during the last 5 years, with the majority of whom the writer has been personally familiar. Ten of the patients showed clinical evidence of coronary sclerosis and 4 of these had coronary thrombosis. There were 15 patients having the diagnosis of arteriosclerotic heart disease, without specific evidence of coronary thrombosis. Only 5 presented the anginal syndrome. There were 7 patients having definite heart failure with either acute or chronic passive congestion. In 4 instances auricular fibrillation was present, one of these instances occurring in the postoperative period.

There were 4 patients in the 6th decade, 7 in the 7th, 11 in the 8th, 2 in the 9th, and 1 in the 10th. All patients were admitted to the hospital while suffering from total retention of urine.

From a study of Table 1, it is seen that 10 patients had a systolic blood pressure of 170 mm. Hg or more at the time of admission to the hospital. Five of these maintained a definite hypertension throughout hospital stay without any significant drop in blood pressure after adequate vesical drainage had been established. These patients are regarded as having definite hypertension. One patient having arteriosclerotic heart disease and auricular fibrillation had a pressure of 125/65 mm. Hg both before and also after drainage. He returned 5 years later having a pressure of 190/100 mm. Hg. Another patient showed no diminution of hypertension after the bladder had been on drainage for 5 years. Such findings may be indicative of two things: (1) there has already been irreparable renal damage before vesical relief is obtained, and (2) a fairly good myocardium is present to maintain such a peripheral blood pressure over such a period of time without heart failure. A significant drop in blood pressure (20 mm. Hg or more) occurred in 10 patients following drainage of the bladder. This fall in blood pressure usually begins within 24 hours after relief of urinary retention. In those cases in which retention has been acute and of short

TABLE 1.—AN ANALYSIS OF 25 CASES OF COËXISTING PROSTATISM AND HEART DISEASE

Case	Age	Cardiac diagnosis	Duration of urinary retention	Mg. % non-protein nitrogen of blood	Blood pressure, mm. of mercury			Days treatment before operation	Operation*	Days in hospital after operation	Result
					Initial	After drainage	At discharge				
1	68	Cor. thrombosis; card. insuff.	2 yrs.	53 37	110/76	90/60	90/60	22	T.P.	8	Improved
2	63	Cor. thrombosis	2 wks.	35 29	120/80	120/80	120/80	24	T.P.	10	Improved
3	57	Arteriosclerotic ht. dis.; auric. fibrill.	3 days	30 30	150/80	130/80	110/60	9	T.P.	21 Pul. embolus	Improved
4	71	Arteriosclerotic ht. dis.; card. insuff.	3 mos.	62 94 41 42	170/80	120/75	135/60	64	Cystotomy T.P.	13	Impr.; died 3 mos. later of pneu.
5	80	Cor. sclerosis; auric. fibrill.; hypertension	10 yrs.	30 46	180/110	..	210/90	..	Cystotomy	25 7 mos. drain.	Impr.; died 5 yrs. later; cbr. thrombosis
6	53	Angina pectoris; arteriosclerotic ht. dis.	1 day	45 32	130/90	115/70	110/70	15	T.P.	26	Improved
7	74	Arteriosclerotic ht. dis.; auric. fibrill.	3 mos.	28 38	125/65	130/65	135/65	74	Cystotomy T.P.	6	Improved
8	72	Arteriosclerotic ht. dis.	18 mos.	109 67 56	105/70	90/60	125/85	365	Cystotomy S.P.	27	Improved
9	79	Arteriosclerotic ht. dis.	8 yrs.	141 77	190/100	130/80	140/80	28	Cystotomy P.P.	5	Dead; renal failure
10	74	Arteriosclerotic ht. dis.	4 yrs.	28 19	155/90	105/60	110/80	23	P.P.	76	Impr.; well 5 yrs. later
11	69	Arteriosclerotic ht. dis.; myocard. insuff.	7 days	28 20	115/75	115/75	120/75	21	S.P.	13	Improved
12	81	Arteriosclerotic ht. dis.; myocard. insuff.	7 days	45 30	135/70	135/70	130/70	11	S.P.	18	Impr.; well 4 yrs. later
13	68	Arteriosclerotic ht.	2 days	25	190/90	160/80	180/90	30	Catheter cystoscopy	..	Impr.; well 1 yr. later

12	81	Arteriosclerotic ht. dis.; myocard. insuff.	7 days	45 30	135/70	135/70	130/70	11	S.P.	18	Impr.; well 4 yrs. later
13	68	Arteriosclerotic ht. dis.; myocard. insuff.	2 days	25 25	190/90	160/80	180/90	30	Catheter cystoscopy	..	Impr.; well 1 yr. later
14	72	Arteriosclerotic ht. dis.; auric. fibrill. pneumonia	1 day	22	170/80	150/90	150/90	3	Transfer to medical	..	Improved
15	72	Arteriosclerotic ht. dis.	12 days	34 26	180/90	140/90	130/80	10	P.P.	30	Improved
16	76	Arteriosclerotic ht. dis.	1 yr.	38 49 60 40	125/80	130/80	110/60	57	Cystotomy S.P.	25	Improved
17	59	Hyperten. ht. dis.; myocard. insuff.	8 yrs. intermittent	95 57	150/110	130/80	130/80	25	Cystotomy	..	Impr.; living 3 yrs. later
18	60	Cor. sclerosis; anginal syndrome	3 years. intermittent	29 29	120/80	120/80	130/80	11	T. and S.P.	37	Impr.; diab. mell.
19	78	Arteriosclerotic ht. dis.	5 wks.	28 42	150/80	115/60	110/60	2	Transurethral resection; cystotomy radon	11	Died; cor. thrombosis
20	58	Cor. (old) thrombosis; angina	3 mos.	37 32	190/80	185/90	180/90	9	P.P.	19	Impr.; diab. mell.
21	66	Arteriosclerotic ht. dis.; angina	4 mos.	38 24	125/70	125/70	130/70	6	P.P.	17	Improved
22	77	Arteriosclerotic ht. dis.	10 days	32 22	115/70	110/70	110/60	16	S.P.	12	Improved
23	91	Arteriosclerotic ht. dis.; myocard. infarct.	30 days	60	140/60	..	135/80	3	T.P.	2	Dead; renal failure
24	76	Cor. sclerosis; hypertension	3 days	60 32	210/110	185/120	160/100	35	Suprapubic prostatectomy	1	Dead; cor. thrombosis
25	69	Cor. sclerosis; myocard. insuff.	6 mos.	38 24	154/70	170/70	160/70	33	Cystotomy	28	Improved

* T.P. = Transurethral prostatectomy. P.P. = Perineal prostatectomy. S.P. = Suprapubic prostatectomy.

duration the change may be immediate. Usually, however, it is a gradual fall over a period of days varying with the condition of the individual patient. While the patient is going through this renal and cardiovascular readjustment, there may be varying degrees of somnolence, weakness, anorexia and even disorientation. The duration of this period is inversely proportional to the efficiency of the myocardium and the renal function. The extent of fall in blood pressure is at times alarming, particularly in patients having definite cardiac disease. However, with proper care the pressure will usually rise again as myocardial efficiency increases and circulatory equilibrium again becomes established. There were 10 patients having a systolic blood pressure of 130 mm. Hg or less who exhibited no change in tension throughout the hospital stay. In general we regard the elderly patient with a low blood pressure as having a poorer outlook than the individual who maintains a pressure which is more usual at his age. The former condition may be a sign of a weak myocardium, or may be due to faulty peripheral circulatory dynamics.

Digitalis was administered to 18 patients and 7 did not require it. In spite of a recent cardiac accident, if there is no evidence of myocardial insufficiency digitalis is not usually employed. However, if there is doubt as to its necessity, the safer procedure is to give the drug.

The renal function tests employed were measurement of the concentrating power of the kidneys, the non-protein nitrogen of the blood, the fluid intake and output, and the excretion of phenolsulphonephthalein and diodrast. Only one of these patients had a fixed low specific gravity of the urine. The non-protein nitrogen of the blood of 14 patients was within normal limits throughout the hospital stay; 11 patients had definite elevation of the non-protein nitrogen at admission and in 6 of these it had become normal at the time of discharge from the hospital. There were 5 patients who exhibited a continual rise of the non-protein nitrogen for several days after vesical drainage was established. Only one of the 25 patients had a phenolsulphonephthalein excretion which could be judged as being within normal limits. Three patients had no excretion of phenolsulphonephthalein that was detectable and 7 had an excretion of less than 35% in 2 hours. Only 7 patients showed a significant increase of excretion of phenolsulphonephthalein during the hospital stay as evidence of improved renal function, yet 21 patients were definitely improved as judged by the clinical condition and by various laboratory tests. This illustrates somewhat the limitation of the value of the phenolsulphonephthalein test as a basis for clinical judgment.

According to the classification that we have used for convenience in the foregoing discussion, these 25 patients are found to be distributed in the following manner: Group 1, 12 patients; Group 2, 4 patients; Group 3, 9 patients.

As to the urologic treatment of these 25 patients, 2 were treated entirely by urethral drainage; cystotomy only was performed for 3; transurethral prostatectomy was done 8 times; perineal prostatectomy 5; and suprapubic prostatectomy 7.

The period of preparation before operation extended from 2 days to 1 year. Two patients, one prepared for 2 days and the other for 3 days before transurethral resection of the prostate, both died within 48 hours after operation of coronary thrombosis. One patient, aged 79, who had perineal prostatectomy after 28 days of suprapubic drainage, died 5 days after operation of renal failure owing to chronic pyelonephritis and nephrosclerosis. The other death occurred 24 hours after suprapubic prostatectomy in a patient aged 76 years. The cause of death was coronary thrombosis. Preoperative preparation lasted 35 days, during which time the non-protein nitrogen of the blood fell from 80 mg. to 32 mg. per 100 cc., but the blood pressure remained at 185/120 mm. Hg. Thus it is seen that even though a long period of preparation be carried out, one cannot always forestall cardiac accidents. However, such careful preparation tends to prevent many of them.

A careful choice of anesthesia and anesthetist is of great importance when the patient having heart disease must undergo a surgical procedure. In general, one wishes in these patients to avoid particularly sudden and extreme changes in blood pressure. The choice of anesthetic is determined for the individual patient by the nature of the operation to be performed and by the emotional stability of the patient. For those who are not apprehensive, a low spinal anesthesia is most suitable for transurethral or perineal surgery. When suprapubic cystotomy is necessary, local anesthesia with 1% procaine without adrenalin is satisfactory after analgesia by morphine. It has also been our experience that such patients tolerate exceedingly well gas-oxygen induction and ether anesthesia. This form is to be preferred for the nervous patient and for those in whom any sudden change in blood pressure would be particularly dangerous, *e. g.*, after a recent coronary thrombosis.

When general anesthesia is used for a patient with heart disease, the time and amount of anesthesia may be greatly reduced by having the patient prepared and in the proper position to begin the operation before induction is started. A quick induction with vinyl ether followed by ethyl ether is satisfactory under these conditions.

In a review of the surgical risk of patients with heart disease Butler, Feeney and Levine[2] have given the surgeon reason to maintain an optimistic attitude toward the results of necessary operative intervention. Of 500 consecutive patients who had prostatectomy in this hospital, there were 62 who had a history and definite signs of heart disease. Sixty-six operations were performed upon this group and there were 3 "unexpected" deaths. It was concluded that with careful cardiac therapy before and after operation, heart

disease itself was rarely a contraindication to necessary, timely prostectomy.

Conclusions. 1. A careful history is most important in eliciting evidence of heart disease.

2. Studies of exercise tolerance and vital capacity are of value in estimating the operative risk of elderly patients.

3. The patient who has recently been able to lead an active life is a good operative risk in spite of the presence of heart disease.

4. Acute urinary retention precipitated by an acute cardiac crisis does not always require subsequent prostatectomy. By careful judicious management it is often possible to tide such patients over by conservative means until cardiac decompensation has cleared and normal micturition been resumed.

5. The patient who tends toward recurrent cardiac decompensation with associated urinary difficulties, has progressively more severe urinary retention with each successive cardiac breakdown.

6. Several weeks should elapse after a coronary accident before resorting to surgery. In general the prognosis is better for these patients who have more than 4 weeks preoperative preparation, but this period must be judged on the basis of the merits of the individual case.

7. It is now more often a choice of the proper time to operate and the kind of operation to be employed rather than a decision for or against surgery, because modern methods do not impose a burden on even the diseased heart sufficient to upset its physiologic function when adequate medical care is given.

8. After prostatectomy great improvement is manifested in the cardiovascular condition of the patient who has had urinary retention and heart disease.

9. The operative approach and anesthesia depend on the characteristics and abilities of the patient, surgeon and anesthetist. In our clinic, the transurethral and perineal approaches have been used in recent years almost entirely, except when there is a definite and special indication for the suprapubic operation. The anesthesia of choice has been low spinal or ether.

10. Though one cannot always anticipate cardiac accidents, much can be done to forestall such events. By means of careful study of the patients in this age group, it is at least possible to designate those who are most likely to develop a cardiac complication and to render to these patients especial attention regarding stabilization of the circulatory system.

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THE MECHANISM OF A FORM OF GLOMERULONEPHRITIS*

NEPHROTOXIC NEPHRITIS IN RABBITS

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NEPHROTOXIC nephritis has been produced in guinea pigs,[8,11] dogs,[3,11] rats,[9,13,14] and rabbits[1,2,4,5,6,10,15] by the injection of antirenal sera. The remarkable clinical, pathologic, and physiologic similarity of this experimental disease to human glomerulonephritis has resulted in extensive investigations. The acknowledged virtue of nephrotoxic nephritis as a medium for investigation has, however, in a measure been dulled by the apparent absence of an analogy between the mechanism of the experimental disease and its counterpart in the human. If one accepts the concept that the experimental nephritis is produced by the direct action of the antibody contained in the nephrotoxic serum upon antigen inherent in the kidney, the only possible analogy that has been drawn is that in both instances—human and animal—the mediating influence is an antigen-antibody reaction.

That the above mechanism is not the cause of nephrotoxic nephritis in rabbits was suggested in a previous report by the author.[6] Nephrotoxic duck serum was prepared by repeated intraperitoneal injections of rabbit kidney tissue into ducks. The injection of this serum into rabbits was followed, after a latent period of from 5 to 8 days, by the onset of nephritis. It was then demonstrated that the onset of the nephritis occurred shortly after the time of appearance of antibodies to duck serum in the circulating blood of the rabbit. In rabbits injected with duck serum, either normal or nephrotoxic, several days or weeks prior to the injection of nephrotoxic serum (the latter injection being preceded by desensitization to avoid anaphylaxis), antibodies to duck serum reappeared rapidly, and the duration of the latent period was shortened. In rabbits exposed to Roentgen rays in adequate dosage, antibodies to duck serum were not formed following the injection of nephrotoxic serum, and nephritis failed to appear. These findings suggested the hypothesis illustrated in Figure 1, a concept strongly supported by the experiments to be described, and one which lends itself to analogy with current concepts of the probable mechanism by which human glomerulonephritis develops.

This concept explains the latent period as the time required for the development of antibodies to duck serum, the shortening of the latent period in previously injected animals on the basis that the formation of antibodies is accelerated, and the failure to develop

* These studies were supported by the George deB. Keim Memorial Fund.

nephritis in rabbits exposed to Roentgen ray on the basis that the formation of antibodies to duck serum is completely inhibited. Although the results of the previous experiments appeared quite definite, it was felt that confirmation of the suggested hypothesis demanded further study, especially with regard to the mechanism by which the exposure of the rabbits to Roentgen ray so profoundly influenced the subsequent effects of the injection of the nephrotoxic serum.

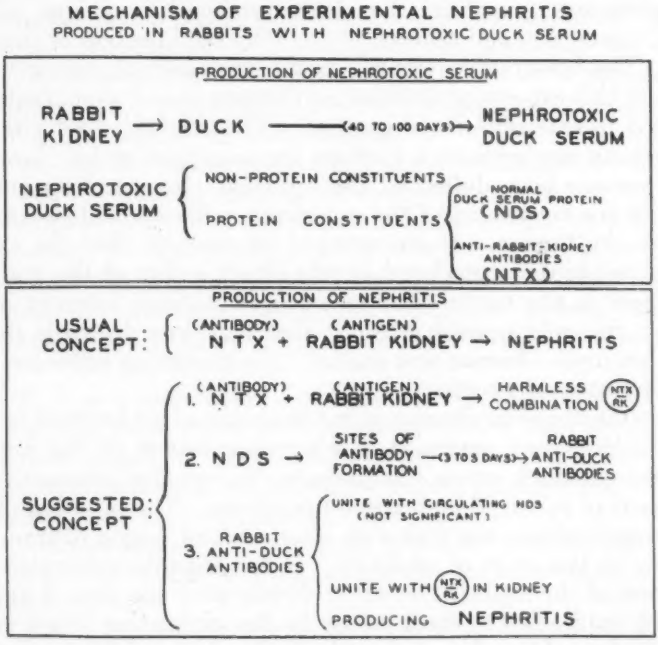
MECHANISM OF EXPERIMENTAL NEPHRITIS
PRODUCED IN RABBITS WITH NEPHROTOXIC DUCK SERUM
PRODUCTION OF NEPHROTOXIC SERUM
RABBIT KIDNEY
DUCK
(40 TO 100 DAYS)
NEPHROTOXIC DUCK SERUM
NEPHROTOXIC DUCK SERUM
NON-PROTEIN CONSTITUENTS
PROTEIN CONSTITUENTS
NORMAL DUCK SERUM PROTEIN (NDS)
ANTI-RABBIT-KIDNEY ANTIBODIES (NTX)
PRODUCTION OF NEPHRITIS
USUAL CONCEPT:
(ANTIBODY) N T X + (ANTIGEN) RABBIT KIDNEY → NEPHRITIS
SUGGESTED CONCEPT
1. (ANTIBODY) N T X + (ANTIGEN) RABBIT KIDNEY → HARMLESS COMBINATION
2. N D S → SITES OF ANTIBODY FORMATION (3 TO 5 DAYS) → RABBIT ANTI-DUCK ANTIBODIES
3. RABBIT ANTI-DUCK ANTIBODIES
UNITE WITH CIRCULATING NDS (NOT SIGNIFICANT)
UNITE WITH IN KIDNEY
PRODUCING NEPHRITIS

FIG. 1.—Mechanism of experimental nephritis, produced in rabbits with nephrotoxic duck serum.

Methods. The same strain of rabbits (mixed Dutch and American Blue) was used as in previous experiments. All weighed between 1700 and 2100 gm. Nephrotoxic serum was prepared by the repeated intraperitoneal injection of Pekin ducks with an emulsion of rabbit kidney. Roentgen ray was administered by a single 40 minute exposure of each entire animal with a total of 480 r.* Anti-duck-serum rabbit serum was obtained from rabbits which had received repeated intracutaneous injections of 0.5 cc. of normal duck serum at 6-day intervals. The formation of antibodies to duck serum and the disappearance of the injected duck serum from the circulation were studied by the precipitative methods previously described.

Results. Nine rabbits were injected with various doses of three different lots of nephrotoxin (NTX). During the 2-day period preceding the injection of the nephrotoxin, designated the desensi-

* Rabbits were treated with Roentgen ray under the direction of Dr. George P. Keefer, Fellow in Radiology, in this hospital.

tization period, all rabbits in these experiments received multiple increasing small doses of normal duck serum. This was done to make the results of these experiments strictly comparable with those of the preceding study where the desensitization procedure was necessary to avoid anaphylactic shock in rabbits reinjected with either normal or nephrotoxic duck serum.

The period of incubation before the development of the nephritis, as in previous observations, ranged from 5 to 8 days. There appeared to be no correlation between the size of the dose and the duration of the incubation period. In animals injected with large doses of NTX lot "B" or NTX lot "AB", abundant albuminuria with a few casts and minimal hematuria appeared immediately after the injection. This "false nephritis" completely disappeared within 48 hours. The urine then remained clear until several days later at the time of the true onset of the nephritis. The results of precipitative studies for the development of antibody to duck serum are shown in Figure 2.

Three rabbits were then exposed to Roentgen ray and injected with comparable doses of nephrotoxic serum. As previously observed in 8 other rabbits, nephritis did not develop, and as shown in Figure 2, no antibodies were formed.

A third group of rabbits were exposed to Roentgen ray, injected with nephrotoxic serum, and then injected with pooled anti-duck serum rabbit serum (ADS). Red blood cells obtained from each rabbit to be injected were tested for agglutination against the serum to be injected. No agglutination was observed. The ADS was administered to each rabbit as follows: 0.1, 0.2, 0.5, 1, 2, 5 cc., respectively at hourly intervals. The following day an initial dose of 2 cc. was followed by 6 cc., then two injections of 10 cc. each. The next day the serum was given in 3 doses of 10 cc. each. In rabbits XA–1 and XA–2 a somewhat different procedure was followed, but the principle of gradually increasing doses was likewise employed. In no instance was there any evidence of anaphylaxis. In the case of rabbits XA–1 and XA–2, the administration of the ADS was started on the day following the injection of the NTX. Nephritis did not develop in these rabbits. The other 4 rabbits of this group were identically injected with ADS on the fifth, sixth and seventh day. In each instance abundant albuminuria with casts and minimal hematuria appeared on the eighth day and persisted until the animal was sacrificed 9 to 12 days later. Grossly the kidneys were swollen and pale, with many punctate hemorrhages over the cortex. The microscopic pathologic changes were indistinguishable from those observed in normal rabbits injected with nephrotoxic serum, though less severe. As shown in Figure 2, changes in the circulating duck serum and antibody were quite similar to those which spontaneously developed in the normal rabbits.

Two rabbits (XR–1 and XR–2) were treated in exactly the same manner as XA–3, 4, 5, and 6, except that normal rabbit serum (NRS) was used instead of the ADS. Nephritis did not develop and precipitation curves were essentially as in the group exposed to

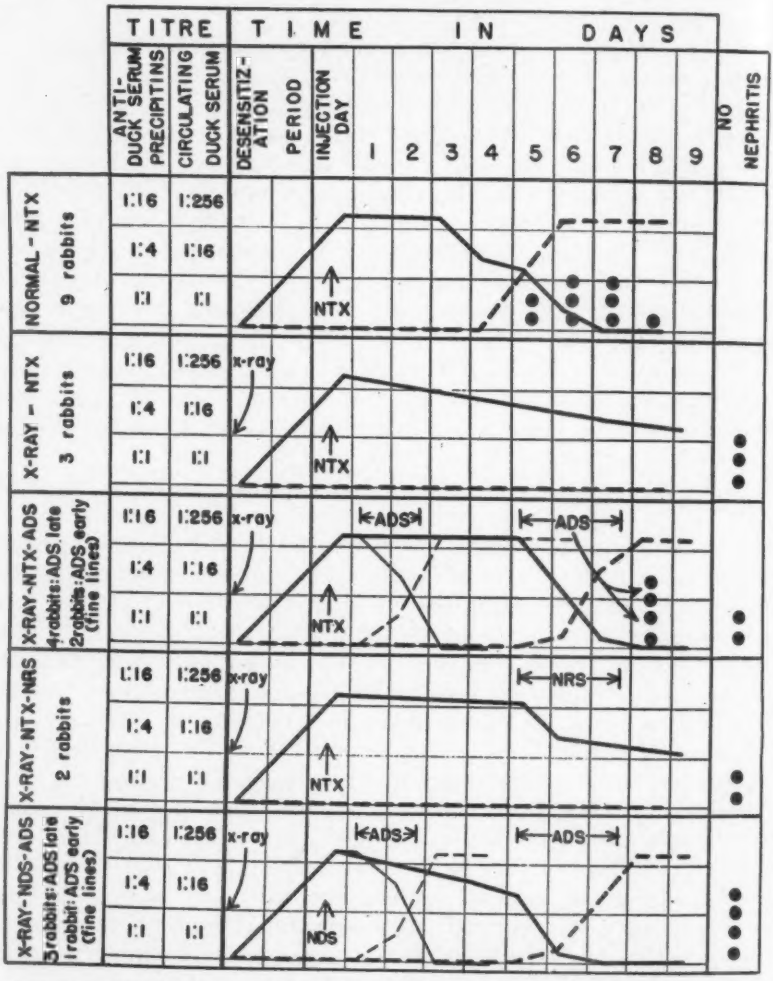

FIG. 2.—Disappearance of circulating duck serum (solid lines), development of precipitins to duck serum (broken lines), and clinical onset of nephritis (each dot represents 1 rabbit).

Roentgen ray and injected with NTX. A "false nephritis" was observed in these rabbits, but was not followed by the onset of the true nephritis.

A fifth group of 4 rabbits was tested in the same manner as the XA series except that normal duck serum (NDS) was given in place

of the NTX. Although the precipitation curves resembled those of the XA series, nephritis did not develop.

TABLE 1.—INFLUENCE OF NEPHROTOXIC DUCK SERUM, ROENTGEN RAY ANTI-DUCK-SERUM RABBIT SERUM, NORMAL RABBIT SERUM, AND NORMAL DUCK SERUM, ADMINISTERED IN VARIOUS COMBINATIONS, UPON THE DEVELOPMENT OF NEPHRITIS.

(Asterisk indicates rabbits in which a "false nephritis" appeared (see text).

				Rabbit serum			Nephritis	
Series	Rabbit No.	Roentgen ray	Duck serum	Day	Cc.	ADS or NRS	Appears	Day
I NTX	N-1	no	5.0 NTX "P"	..	no	..	yes	8
	N-2	no	5.0 NTX "P"	..	no	..	yes	6
	N-3	no	2.2 NTX "P"	..	no	..	yes	5
	N-4	no	6.0 NTX "P"	..	no	..	yes	5
	N-5	no	3.0 NTX "A"	..	no	..	yes	6
	N-6	no	6.0 NTX "A"	..	no	..	yes	6
	N-7	no	3.0 NTX "B"	..	no	..	yes	7
	N-8	no	6.0 NTX "B"	..	no	..	yes	7*
	N-9	no	5.5 NTX "AB"	..	no	..	yes	7*
II Roentgen ray: NTX	X-1	yes	6.0 NTX "P"	..	no	..	no	
	X-2	yes	6.0 NTX "P"	..	no	..	no	
	X-3	yes	6.0 NTX "A"	..	no	..	no	
III Roentgen ray: NTX: ADS	XA-1	yes	6.0 NTX "P"	1	20	ADS	no	
				2	40	ADS		
	XA-2	yes	6.0 NTX "P"	1	25	ADS	no	
				2	60	ADS		
	XA-3	yes	6.0 NTX "A"	5	8.8	ADS	yes	8
				6	28	ADS		
				7	30	ADS		
	XA-4	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
				7	30	ADS		
	XA-5	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
				7	30	ADS		
	XA-6	yes	5.5 NTX "AB"	5	8.8	ADS	yes	8*
				6	28	ADS		
				7	30	ADS		
IV Roentgen ray: NTX : NRS	XR-1	yes	5.5 NTX "AB"	5	8.8	NRS	no	*
				6	28	NRS		
				7	30	NRS		
	XR-2	yes	5.5 NTX "AB"	5	8.8	NRS	no	*
				6	28	NRS		
				7	30	NRS		
V Roentgen ray: NDS : ADS	XNA-1	yes	5.5 NDS	1	20	ADS	no	
				2	40	ADS		
	XNA-2	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		
	XNA-3	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		
	XNA-4	yes	5.5 NDS	5	8.8	ADS	no	
				6	28	ADS		
				7	30	ADS		

For additional rabbits in Series 1 and 2, similarly treated and studied, with identical results, see Reference 6. The author had intended to include additional animals in each of the three lower groups. This was prevented by the accidental destruction of some of the necessary sera. Conclusions, however, seem valid in view of the complete uniformity of results in rabbits similarly treated.

A summary of these experiments is shown in Table 1. It is seen that nephritis developed in rabbits exposed to Roentgen ray, injected with nephrotoxic serum, an interval allowed to elapse, and then injected with anti-duck serum. Nephritis did not develop when normal rabbit serum was substituted for anti-duck-serum rabbit serum or when normal duck serum was substituted for nephrotoxic serum.

Discussion. These experiments appear to complement those previously reported in establishing the mechanism illustrated in Figure 1 as that which is operative in the production of nephrotoxic nephritis in rabbits. Antibodies were passively transferred to attack an antigen combined in the kidney, whereas in the normal rabbit injected with nephrotoxic serum, the antibodies are formed by the rabbit, attacking the antigen combined in the kidney. In view of the demonstration[6] that the nephrotoxic component can be removed by the simple perfusion of the nephrotoxic serum through a rabbit kidney, it is of interest to note that the nephritis does not develop when the anti-duck serum injections are started 24 hours after the injection of the nephrotoxin. This would appear to indicate that the nephrotoxic component, though bound to the kidney, had not yet become incorporated into or combined with the kidney cells, and hence was destroyed by the anti-duck antibodies without renal damage. Analogy may be made with the many observations that a time interval is required between the injection of antigen and the injection of antibody for successful passive transfer anaphylaxis.

The failure of nephritis to develop in rabbits exposed to Roentgen ray, injected with nephrotoxic serum, and then with normal rabbit serum appears to eliminate the possibility that Roentgen ray may destroy complement and thus prevent an antigen-antibody reaction. From the fact that nephritis was not induced by the passive transfer of anti-duck antibodies in rabbits injected with normal duck serum it is apparent that a non-specific reverse anaphylaxis was not an essential factor.

With the exception of the guinea pig, in which the response to the injection of nephrotoxic serum is complicated by hemolytic and anaphylactic phenomena,[8,11] the one striking variation in the nephritic response of the different species of animals in which nephrotoxic nephritis has been studied is in the duration of the latent period between the time of injection and the time of onset of the nephritis. A latent period of at least 5 days has been uniformly observed in rabbits injected with nephrotoxic duct serum. A latent period of 6 to 10 days was noted by Fouts, Corcoran, and Page[3] in dogs injected with nephrotoxic serum prepared in the hen. The mechanism demonstrated here as the cause of nephritis in rabbits would appear applicable by analogy to these dogs. The concept cannot, however, be applied without modification to nephritis produced in rats by the injection of nephrotoxic rabbit serum,[9,13,14] or to the nephritis produced in dogs by the injection of nephrotoxic rabbit serum,[11] for

in these instances renal changes appear within a few hours after the injection of the serum. In our experiments occasional lots of nephrotoxic serum were found to produce a "false nephritis" within a few hours after the injection—massive albuminuria with casts and a very few red blood cells. These urinary abnormalities completely disappeared, to reappear several days later with the onset of the true nephritis, unless the mechanism responsible for the latter were suppressed by the use of Roentgen ray. This phenomenon was likewise observed by Fouts, Corcoran, and Page[3] in dogs. Consideration must be given to the possibility that the apparent absence of the latent period in rats and in Pearce's dogs was due to an imperceptible blending of a "false nephritis" into the true nephritis. If so, urinary abnormalities should rapidly disappear in animals exposed to doses of Roentgen ray adequate to inhibit antibody formation. It may or may not be mere coincidence that nephrotoxic sera derived from rabbits produce an immediate response (in guinea

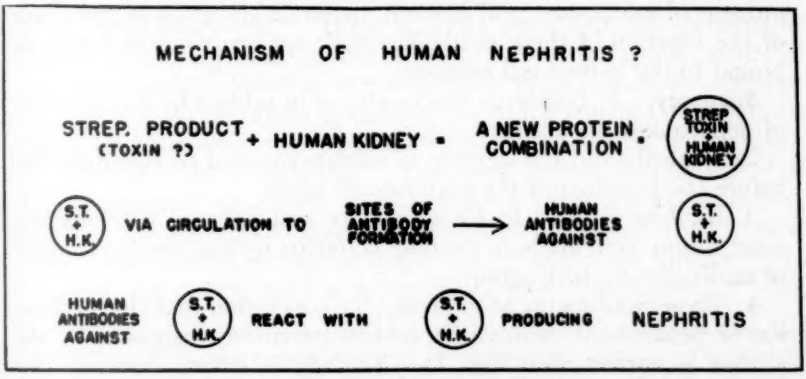

FIG. 3.—Suggested concept of the mechanism of human glomerulonephritis (see text).

pigs, rats, and dogs), whereas sera derived from fowl (duck, hen) are associated with a latent period (in rabbit and dog).

An interesting concept of an antigen-antibody mechanism as the cause of acute glomerulonephritis in man has been recently introduced by Schwentker and Comploier.[12] They suggested that renal cell proteins are altered by some product of the streptococcal infection, and that this altered renal protein constitutes a new antigen, introduced into the circulation as the damaged renal cells are repaired. As a result, antibodies are produced which react with the altered renal proteins, and possibly also with normal renal proteins through an immunologic relationship to which the term hapten is applied, to produce nephritis (Fig. 3).

This concept offers a more nearly satisfactory interpretation of the clinical characteristics peculiar to human glomerulonephritis than any concept suggested heretofore; and it is not at variance with known facts in any basic particular. It offers an explanation for

the rôle of streptococci, for the latent period between the infection and the onset of the nephritis, for the shortening of the latent period in exacerbations of the disease, and for the absence of bacteria in the nephritic kidneys. It is, however, based more upon circumstantial evidence and analogy than upon factual support. Kay, Lucchesi, and Rutherford[7] were unable to demonstrate antibodies to human kidney antigens in the sera of a large group of patients with scarlet fever. The negative results obtained, while failing to give support to the concept, could by no means be considered a conclusive test of the validity of the concept for reasons discussed in their presentation. The mechanism of nephrotoxic nephritis, here described, may be considered to offer some further support, by analogy, for the concept of Schwentker and Comploier.[12] In the rabbit, antigen is bound to or combined with the kidney cells because of an immunologic affinity. In man, the antigen is formed in the kidney by the action of some product of the streptococcal infection upon the kidney cells. In both animal and man, a latent period ensues for the development of antibodies, and in both, nephritis develops as the result of the reaction of these antibodies with antigen combined with or bound to the kidney cell proteins.

Summary. 1. Nephritis was produced in rabbits by the injection of nephrotoxic duck serum.

2. Nephritis did not develop in rabbits exposed to Roentgen ray before the injection of the nephrotoxic serum.

3. Rabbits exposed to Roentgen ray and injected with nephrotoxic serum were made to develop nephritis by the passive transfer of antibodies to duck serum.

4. These results appear to justify the conclusion that the mechanism of nephrotoxic nephritis in rabbits previously suggested by the author is correct (see Fig. 1). Analogy is drawn between this mechanism and recent concepts of the mechanism by which human glomerulonephritis develops.

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NON-DIABETIC GLYCOSURIA

A Follow-up Study with Glucose Tolerance Tests

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It is the purpose of this paper to present the results of our studies upon selected cases with glycosuria in order to determine the prognostic significance of apparently non-diabetic glycosuria.

It has been repeatedly stated that non-diabetic glycosuria is without serious consequences. Marble, Joslin, Dublin and Marks[8] state that "Non-diabetic glycosuria in itself has little or no adverse influence upon longevity." These authors point out the paramount importance of adequate initial study to establish the true nature of the glycosuria. John[4] is of the opinion that "There is sufficient evidence in the literature to support the statement that non-diabetic glycosuria remains so throughout the years. . . . and is not a transitory state toward diabetes." Lawrence[7] writes as follows: "If normoglycemic glycosuria is proved by a thorough investigation, such as the finding of a normal glucose tolerance test, then I think the whole condition can be neglected at once and forever." In general, our studies tend to substantiate these statements.

Methods. Subjects were chosen from a group of individuals who had submitted to glucose tolerance tests 5 to 13 years ago because of a previous finding of glycosuria in the course of an examination for life insurance. Most of the subjects selected for follow-up had clearly normoglycemic curves with glycosuria, but a few borderline glucose tolerance curves are included for comparison. One hundred and nine individuals were invited to participate but only 32 accepted. Five additional cases could be followed up from existing records. The majority of cases were restudied with the conventional 1-dose, 2-hour test employing 1 dose of 50 gm. of glucose. A few cases recorded in the latter portion of Table 1 were studied by the Exton-Rose, two-dose technique[1] in both the original study and the follow-up or they may have received the 1-dose test in 1 instance and the 2-dose in another.

Interpretation of Blood Sugar Values. Capillary blood sugar values are reported throughout Table 1 because these were used in all the original studies. Capillary blood sugar values may be unpredictably higher than simultaneously determined venous blood sugar values especially during the peak of the curve at ½ or 1 hour. This is true both in the conventional 1-dose technique or in the 2-dose Exton-Rose technique. Two hours after the ingestion of glucose the capillary and venous blood sugar values are often nearly the

TABLE 1.—FOLLOW-UP STUDY OF NON-DIABETIC GLYCOSURIA

(One-dose, 2-hour glucose tolerance test used except in those cases marked with an asterisk, which indicates a 1-hour value of the 2-dose, 1-hour technique, Exton-Rose)

		Original study					Follow-up study				
			Blood sugar tolerance, mg. per 100 cc.					Blood sugar tolerance, mg. per 100 cc.			
	Subject	Date	Fasting	½-hour	2-hour	Glycosuria, %	Date	Fasting	½-hour	2-hour	Glycosuria, %
1	E. P. W.	7–13–31	113	190	125	0.5	2–19–37	105	200	66	+
2	L. R.	8–15–34	65	130	80	3.0	8–25–39	120	140	95	1.0
3	G. M.	3–10–34	106	171	88	+	3–17–40	85	175	92	0.4
4	R. S. M.	3– 9–37	88	157	80	3.0	12–30–40	76	..	93	2.0
5	J. P.	2–26–29	110	206	70	+	4–28–41	110	190	95	0.5
6	E. D. B.	12–10–29	114	180	96	0.5	6– 2–41	100	190	123	1.0
7	J. W. W.	1–28–30	105	206	71	+	5–14–41	78	143	90	1.0
8	E. L. S.	9–25–30	100	196	127	+	7–19–41	75	112	130	0.5
9	G. S. M.	7–14–31	109	171	147	0.4	6– 3–41	90	133	83	0.3
10	W. H. B.	1–26–32	99	178	118	1.0	5–13–41	110	168	185	10.0
11	J. H. M.	4– 7–32	91	167	121	0.2	6–25–41	82	162	110	0.5
12	H. S.	7– 5–32	92	155	96	0.5	6–11–41	80	120	70	0.2
13	J. P. G.	10–19–32	110	158	145	1.0	5–27–41	110	198	105	1.5
14	W. B.	2– 9–33	97	123	133	0.4	6–25–41	90	115	83	0.0
15	D. H. W.	3–31–33	95	121	101	1.0	6–18–41	90	132	97	0.5
16	O. W.	8– 8–33	93	161	86	0.5	5–10–41	75	102	60	0.3
17	J. M.	9–22–33	91	182	108	1.0	6–18–41	92	103	73	0.0
18	M. M.	11–17–33	98	167	146	0.2	6–26–41	120	230	185	3.0
19	M. S.	3–27–33	..	153	74	0.4	5–27–41	88	138	94	0.5
20	H. W. M.	12–13–33	112	270	132	1.0	7– 6–41	85	183	93	0.2
21	A. R.	7–31–34	109	155	88	0.4	5–15–41	88	134	82	0.5
22	E. H. E.	12– 2–35	80	174	100	0.5	6–22–41	96	135	92	0.5
23	F. H. O.	12– 9–33	110	161	95	1.0	8–16–41	90	136	97	3.0
24	G. H. H.	5–31–33	80	180	99	1.0	8–16–41	95	176	105	5.0
25	S. C. H.	6–20–31	114	168	157	0.3	8–14–41	83	115	121	0.0
26	J. M.	12–11–34	80	125	85	1.0	1–17–42	75	140	70	4.0
27	T. J. B.	6–29–30	90	204	95	+	1– 6–42	95	145	80	0.0
28	A. H.	2–27–37	80	138	80	+	2–25–42	100	145	80	0.5
29	D. F. B.	9–21–29	80	145	80	3.0	Known glycosuria since 1924. Recent fasting blood sugar, 84 mg.				
		1– 7–32	83	208	83	2.0					
30	R. O.	6–25–36	92	148	160*	0.3	7–29–41	100	195	155*	0.5
31	J. V. L.	3– 3–37	80	150	180*	4.0	8– 5–41	78	130	135*	0.3
32	F. C. B.	8– 3–36	88	142	152*	1.5	3–19–41	85	199	173*	0.5
33	W. H. D.	6–18–36	90	150	146*	0.5	8–12–41	90	140	154*	0.4
34	E. S.	12–26–34	100	210	105	0.3	8– 1–41	95	203	273*	3.0
35	L. C. S.	12–15–34	97	157	110	0.5	5– 8–41	94	150	140*	0.5
36	L. D.	12–17–35	100	160	180*	1.0	7–30–41	80	180	60	0.5
37	H. J. R.	5–22–36	95	150	155*	1.0	8–11–41	97	195	200	5.0

same although the capillary blood sugar may be 10 or even 20 mg. per 100 cc. higher than the venous blood sugar. At any rate, one may be sure that the capillary blood sugar will always be higher than the venous blood sugar except in severe diabetes with which we are not dealing here. In this study, venous and capillary blood sugar values were determined simultaneously in many of the follow-up studies; and in each of the 4 individuals (Cases 10, 18, 34 and 37) to be discussed later, who ultimately developed abnormal glucose tolerance responses, the diagnosis was substantiated by the venous blood sugar values.

Criteria. Based upon our previous experience with a comparison of capillary and venous blood sugar values[5] and a consideration of criteria for interpretation of the two types of glucose tolerance techniques which we reviewed in a previous paper,[6] we offer the following criteria for the interpretation of the 1-dose, 2-hour test using capillary blood: For a clearly normal response, a fasting blood sugar of 120 mg. per 100 cc. or less, a ½-hour value of 200 mg. per 100 cc. or less, and a 2-hour value of 120 mg. per 100 cc. or less. These criteria for capillary blood may appear to be rather severe when one considers the fact that capillary blood sugar values may be much higher than venous blood sugar during the postabsorptive period. However, this difference is so variable and unpredictable that the only safe procedure is to consider a blood sugar tolerance curve which exceeds the above-mentioned criteria as being potentially abnormal.

Criteria for the 2-dose test using capillary blood are even more difficult to define but we have selected 180 mg. per 100 cc. or less for the hour value as a normal response for capillary blood providing the fasting sugar is also normal, the amount of rise or fall during the second half hour is not taken into consideration.

Results. Of the 37 cases that were restudied after a period of 5 to 13 years, 4 developed abnormal glucose tolerance curves. In 1 of these (Case 18) the original study had resulted in a borderline blood sugar curve although a 2-hour value of 146 mg. per 100 cc. of capillary blood may be seen in a non-diabetic individual. In the other 3 (Cases 10, 34 and 37) the blood sugar figures were definitely within normal limits at the time of the original examination although 1 (Case 10) had a 2-hour value at the upper limit of normal and another (Case 34) had a ½-hour value that was somewhat high. On the other hand, many of the individuals who did not develop diabetes had original blood sugar curves as high or higher than those individuals whose blood sugar tolerance curves were abnormal on follow-up study.

The percentage of sugar excreted in the urine seemed to be of no prognostic value, indeed, curiously enough, in the individuals we studied those who excreted the most sugar did not develop diabetes (see Table 1).

Discussion. As early as 1922 Holst[3] found the causes of non-diabetic glycosuria to be an abnormally low renal threshold, high alimentary rise, or a combination of the two. Marble and Joslin's[8] definition of true renal glycosuria requires the presence of glucose in fasting as well as postprandial urine, an unusual condition. The great majority of non-diabetic glycosurias have a threshold that is exceeded only after the ingestion of a moderate amount of carbohydrates. None of our subjects would qualify as renal glycosuria according to Joslin's definition. With regard to intermittent and continuous glycosuria Fischer[2] feels that it seems unnecessary to separate arbitrarily the two types of renal glycosuria for they are benign, frequently familial and are differentiated only by the height of the renal threshold for glucose. Regardless of one's classification of non-diabetic glycosuria it is the consensus of opinion that the condition is benign. John[4] in a summary of the literature has shown that individuals may put out large quantities of sugar for years without detriment to themselves. Our results are in agreement with this finding (Table 1). Thus it is evident that the excretion of a large amount of sugar is not necessarily associated with an unfavorable prognosis. When one obtains an unequivocally normal blood sugar tolerance curve especially on more than one occasion it seems unimportant whether the individual has little or much glycosuria. The amount of glycosuria with normal postabsorptive blood sugar levels is purely and simply a function of the renal threshold for glucose. In discussing non-diabetic glycosuria, Marble, Joslin, Dublin and Marks[8] state: "Caution must be advised against accepting as normal, tolerance curves which either at the highest point or subsequent fall are on the borderline of the type found in mild diabetes." We believe that the importance of this cannot be overemphasized and in our experience this statement is equally true whether there is glycosuria or the urine is sugar-free. Any borderline glucose tolerance curve should be rechecked by a repetition of the test after all the factors which may have influenced it have been considered and corrected.

Of the 109 cases of glycosuria with normal or borderline glucose tolerance tests which we attempted to follow-up, 8 could not be contacted because of incorrect addresses, 19 did not reply to two or more letters, 35 either declined to have the study done or accepted but failed to keep their appointment for the test, of these at least 3 are known to have developed diabetes, 10 of the individuals had died, but in none of these was diabetes mentioned as a contributing cause of death, and 37 yielded the information which is summarized in Table 1. All the individuals in the group studied were symptom-free and considered themselves in good health, even those with apparent diabetes.

An interesting question presents itself. Why did 3 individuals with normal blood sugar curves out of a group of 36 cases of glyco-

suria develop probable diabetes? This is much higher than the average chance of developing diabetes. Several possibilities suggest themselves: 1, Obviously a technical error in the original study may have occurred in the determination of the blood sugar curve. 2, The reason for performing the original study was the previous finding of glycosuria; this may have been due to a diminished ability to metabolize glucose. Repeated glucose tolerance curves upon the same individual will show considerable variation. The original glucose tolerance curves in our study may have been performed at a time when a coincidence of favorable circumstances produced a tolerance curve within top normal limits in a very mild diabetic with a lower than average renal threshold for glucose. This possibility emphasizes the need for more than one tolerance study in the evaluation of this type of case. 3, High peak values which some observers consider to be of prognostic significance may have been missed by taking specimens at only ½ and 2 hours. 4, Our study tends to disprove the possibility that the diabetic organism has more tendency to excrete glucose than a normal individual at a given blood sugar level. In fact, this possibility seems very unlikely since both mild diabetics with only moderately elevated blood sugar levels and severe diabetics with high blood sugar levels may fail to excrete glucose due to a high renal threshold for glucose.

Whatever the reason, it seems to be a fact that when conclusions are drawn from a single glucose tolerance test, an individual with apparently non-diabetic glycosuria is more likely to develop diabetes than a normal individual. This has also been the experience of Marble *et al.*[8]

Summary. 1. In a group of 37 individuals with apparently non-diabetic glycosuria, based upon one glucose tolerance curve obtained 5 to 13 years ago a greater number developed diabetes than can be accounted for on the basis of chance.

2. The amount of glucose in the urine was, in itself, of no prognostic significance.

3. If glycosuria is proven by thorough study and continued observation to be truly non-diabetic, it appears to be without detriment to health.

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A QUANTITATIVE STUDY OF THE VARIATIONS IN MULTIPLE STERNAL MARROW SAMPLES TAKEN SIMULTANEOUSLY

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The early investigators[1,4,7] of sternal puncture regarded the procedure as a qualitative one. Bone marrow smears were examined for cellular content just as the pathologist examines any other aspirated fluid. During the years that followed, sternal puncture became increasingly popular, and a large literature on the subject arose. Many modifications of technique were suggested, as is usually the case with a new procedure. Quantitative determinations[2,3,9,10,11] of the different marrow constituents were emphasized with increasing frequency, until the marrow is now studied with the same care and precision as the peripheral blood. Certain workers[6] have gone so far as to develop fixed ratios between the various types of marrow cells, and to attempt to draw conclusions from variations in these ratios. These studies would correspond to the Arneth and Schilling indices for the peripheral blood. Unfortunately, the material aspirated by sternal puncture is not like the blood, and cannot be studied with the same degree of accuracy. The peripheral blood is homogeneous throughout the body, and it is to be expected that a quantitative determination made from any accessible region would be accurate. That this is the case is shown by the fact that multiple samples taken simultaneously from different places check very closely when studied quantitatively.

In marrow studies we find certain inherent fundamental discrepancies which make accurate quantitative determinations impossible. The interior of the sternum is composed of spongy bone, in the interstices of which, the marrow cells are held as a loose tissue. The peripheral blood circulates freely throughout the interior of the sternum in channels called sinuses. The cellular structure of the marrow is not uniform, since it is composed of different groups of cells, namely, granulocytes, erythroid cells and megakaryocytes. These cells are arranged in clusters of a similar type. When a needle is forced into the marrow cavity, admission is made possible by the penetration of the cortical bone and breaking down of some bone spicules. The puncture site is open to variation, as is also the depth to which the needle is inserted. The degree of suction employed cannot, of necessity, always be the same, and the amount of peripheral blood aspirated is very often dependent on conditions within the sternum. The existence of these factors makes it obvious that the aspirated material could

not be homogeneous like the peripheral blood. It seems permissible to make qualitative studies on this material just as with tissue, and, to some degree, rough quantitative determinations as previously pointed out.[8] In order to substantiate this contention, the following experiment was devised and carried out.

Method. A series of 26 patients was selected for study. From each of these 4 samples of marrow were taken. This was accomplished as follows: 2 sternal punctures were done at the same time on each patient, 1 immediately following the other. One puncture was made in the second interspace, the other in the third. From each puncture 2 separate marrow samples were aspirated and labeled Ia, Ib, IIa and IIb. Each sample consisted of 2.5 cc. of fluid which was placed in a tube containing 0.5 cc. of 1.4% sodium oxalate solution evaporated to dryness, to prevent coagulation. Direct smears on slides were also made from each sample at this time. Total nucleated cell counts were done on each sample, and the slides were stained with Jenner-Giemsa stain, after which differential counts of 500 cells were done. The counts were all done by one of us (C. R.). A total white count of the peripheral blood was also done in each case. These data were then tabulated and subjected to statistical analysis.* The tables follow (pp. 498–501).

Discussion. Table 2 shows for several groups of diseases the mean and standard deviation for the total nucleated white cell count and number of polys. Except for diseases of the blood-forming organs, the number of observations in each group was small, and the average of the samples obviously has little meaning except for a study of the variability. The highest mean and standard deviation for the total white count was observed among diseases of the nervous system which included 2 cases with relatively high counts, and 1 case with low counts. The highest and most variable average number of polys was observed in the largest group, *i. e.*, among diseases of the blood-forming organs.

Since an inspection of the individual counts seemed to indicate that there was often as great a variation between cases of the same group, the statistical comparisons were made of the standard deviations from the mean of the 2 samples and 4 samples from the same case. Table 3 shows the standard deviation from the mean white cell count for the two counts from the same sample (pairs) compared with the standard deviation from the mean of four counts from 2 samples taken simultaneously (quartettes). For diseases of the blood-forming organs the standard deviations for the pairs of counts is 9583 ± 611 cells and for the four counts $11{,}619 \pm 740$ cells with a difference only twice its probable error or 2035 ± 960. The standard deviation from the mean of all the counts from the same group as shown in Table 3 was $25{,}426 \pm 1620$ cells which differed from the standard deviation from the mean of four counts from the same case by $13{,}807 \pm 1782$ cells or a difference which is nearly

* The authors wish to thank Dr. W. F. Dunning and Dr. M. R. Curtis of the Crocker Institute, Columbia University, for their help in analyzing the data and interpreting the results.

TABLE 1.—ABSOLUTE NUMBERS FOR MULTIPLE SAMPLES OF STERNAL MARROW

Case No.	Age	Sex	Diagnosis	Red cell count (millions per c.mm.)	White count of peripheral blood (thousands per c.mm.)	Marrow sample	Total nucleated cell count (thousands per c.mm.)	Neutrophil, mature	Neutrophil bands	Metamyelocytes	Neutrophil myelocytes and premyelocytes	Eosinophilic myelocytes	Myeloblasts	Eosinophils	Monocytes	Lymphocytes	Lymphoblasts	Basophils	Plasma cells	Proerythroblasts	Erythroblasts	Normoblasts	Megaloblasts
1	36	M	Chronic arthritis	3.8	13.2	Ia	37.0	12,506	8,214	1.258	3,996	370	222	962	222	1,998	0	0	0	0	4,884	2,368	0
						Ib	45.0	12,960	12,600	720	6,390	360	540	1,800	360	1,980	0	180	0	180	4,590	2,340	0
						IIa	104.0	29,536	18,928	2,912	23,083	1,664	208	4,368	416	208	0	0	0	0	15,600	7,072	0
						IIb	60.0	15,600	15,840	2,400	9 600	600	600	1,920	240	3,600	0	240	0	120	4,200	5,040	0
2	32	F	Pernicious anemia	3.9	9.8	Ia	35.6	16,447	4,130	854	2 990	0	0	356	0	3,062	0	0	0	0	3,774	3,987	0
						Ib	42.0	18,228	5,460	924	5,292	0	84	336	84	1,764	0	0	0	0	4,872	4,956	0
						IIa	57.4	17,679	13,432	2,066	8,840	115	1492	115	0	4,607	0	230	0	0	4,133	4,592	0
						IIb	38.0	15,200	9,424	1,824	3,192	0	380	304	0	2,508	0	0	0	0	1,140	4,028	0
3	57	F	Secondary anemia	3.5	7.8	Ia	39.4	15,524	5,122	1,655	3,782	315	79	315	630	2,049	0	0	0	236	6,383	3,310	0
						Ib	19.2	8,563	2,381	192	2,266	38	0	115	0	499	0	0	0	77	2,573	2,496	0
						IIa	22.0	3,080	3,916	352	6,248	396	0	220	0	1,408	0	44	0	352	2,244	3,740	0
						IIb	20.6	6,221	3,090	1,071	5 315	288	0	618	0	1,277	0	0	0	165	1,112	1,442	0
4	41	F	Gangrene of fingers	4.2	12.0	Ia	118.0	29,028	29,028	8,260	17,228	1,652	1416	2,124	0	3,776	0	0	236	944	1,156	12,744	0
						Ib	81.0	21,384	23,976	7,938	8,910	486	486	2,592	162	3,888	0	0	162	0	5,022	5,994	0
						IIa	60.0	20,160	13,680	4,800	10,800	720	0	1,200	120	1,080	0	0	240	120	3,960	3,120	0
						IIb	133.0	28,196	26,068	7,980	25,536	3,458	532	5,054	266	532	0	0	0	266	17,290	17,822	0
5	47	M	Cirrhosis of liver	5.3	10.8	Ia	40.0	18,160	4,480	720	3,360	0	160	640	400	5,280	0	0	80	80	3,040	3,600	0
						Ib	29.0	11,948	5,336	986	3,364	116	174	174	58	2,378	0	0	0	0	1,102	3,364	0
						IIa	42.0	14,616	7,476	1,680	6,636	0	756	252	420	4,368	0	84	0	336	1,344	4,03[illegible]	0
						IIb	35.0	14,770	6,160	490	6,650	70	210	420	560	1,050	0	0	0	0	2,170	2,45[illegible]	0
6	45	F	Pernicious anemia	4.0	9.8	Ia	23.4	7,722	4,352	1,498	2,855	328	140	374	281	983	0	0	47	234	2,574	2,012	0
						Ib	22.2	8,924	3,508	488	2,886	178	133	222	622	2,042	0	44	44	0	2,042	1,06[illegible]	0
						IIa	52.2	21,706	8,960	2,870	6,627	715	210	1,215	420	3,360	0	0	0	0	3,360	3,[illegible]	0

5	47	M	Cirrhosis of liver	5.3	10.8	Ia	40.0	18,160	4,480	720	3,360	0	160	640	400	5,280	0	0	80	80	3,040	3,600	0
						Ib	29.0	11,948	5,336	986	3,364	116	174	174	58	2,378	0	0	0	0	1,102	3,364	0
						IIa	42.0	14,616	7,476	1,680	6,636	0	756	252	420	4,368	0	84	0	336	1,344	4,03[illegible]	0
						IIb	35.0	14,770	6,160	490	6,650	70	210	420	560	1,050	0	0	0	0	2,170	2,45[illegible]	0
6	45	F	Pernicious anemia	4.0	9.8	Ia	23.4	7,722	4,352	1,498	2,855	328	140	374	281	983	0	0	47	234	2,574	2,012	0
						Ib	22.2	8,924	3,508	488	2,886	178	133	222	622	2,042	0	44	44	0	2,042	1,06[illegible]	0
						IIa	53.2	21,706	8,299	2,979	6,597	745	213	1,915	638	2,660	0	0	0	319	5,958	1,17[illegible]	0
						IIb	45.2	13,922	9,402	3,254	7,684	362	362	814	0	2,441	0	0	0	90	3,616	3,254	0
7	54	F	Pernicious anemia	4.5	10.0	Ia	12.0	7,296	1,752	96	1,248	0	168	72	336	432	0	0	0	0	336	264	0
						Ib	15.4	7,392	3,142	493	2,464	123	185	62	400	246	0	0	0	31	616	246	0
						IIa	12.2	8,150	1,049	0	1,659	24	24	73	488	317	0	0	0	24	268	122	0
						IIb	15.0	8,520	2,100	300	1,920	60	60	240	690	390	0	0	0	0	540	180	0
8	11	M	Congenital lues	4.5	6.4	Ia	66.8	10,955	10,020	1,737	7,214	401	2004	134	0	14,295	0	134	0	134	12,826	6,680	267
						Ib	62.0	20,460	13,268	3,100	6,324	124	620	496	372	4,836	0	124	0	372	7,440	4,464	0
						IIa	78.0	17,160	9,828	4,056	10,608	156	624	780	156	4,836	0	0	0	1872	16,224	11,700	0
						IIb	34.4	9,426	7,430	1,514	3,784	344	413	550	0	3,509	0	0	0	344	3,715	3,371	0
9	11	M	Trichinosis	4.4	15.6	Ia	88.0	15,312	9,328	4,400	10,384	11,616	880	17,072	0	2,816	0	352	0	880	10,208	4,752	0
						Ib	41.8	7,022	6,103	1,087	3,511	2,174	418	15,048	167	2,257	0	84	0	167	2,592	1,170	0
						IIa	77.0	13,552	12,628	2,772	15,092	8,932	616	14,938	0	0	0	462	0	308	6,776	924	0
						IIb	106.0	14,204	19,292	3,604	16,536	6,360	2544	24,380	848	3,180	0	0	0	424	5,512	8,904	212
10	60	M	Hemiplegia	4.5	11.0	Ia	57.4	24,567	11,480	2,066	6,544	230	0	574	0	4,592	0	0	230	344	4,822	1,952	0
						Ib	128.0	47,104	36,608	3,584	19,200	1,536	0	2,304	0	2,816	0	0	0	512	7,168	7,168	0
						IIa	86.0	30,444	20,984	4,816	11,524	688	172	860	0	7,396	0	0	0	516	2,752	5,848	0
						IIb	72.0	32,832	17,856	2,016	7,776	288	144	1,584	0	4,608	0	0	0	144	1,728	3,024	0
11	20	M	Lymphadenitis	4.4	5.6	Ia	50.0	19,100	9,800	1,200	5,000	400	500	800	100	3,100	0	0	0	300	3,100	6,600	0
						Ib	38.0	12,008	9,728	2,052	5,396	304	304	0	0	4,104	0	0	0	76	1,520	2,280	228
						IIa	54.0	19,764	11,988	1,188	5,832	432	432	972	0	5,400	0	324	0	432	2,484	4,752	0
						IIb	45.0	18,270	10,440	630	6,660	360	720	630	630	1,800	0	0	0	180	2,790	1,890	0
12	41	F	Hepatosplenomegaly	4.2	10.0	Ia	9.2	4,195	754	110	662	37	37	221	570	1,251	0	18	0	18	607	718	0
						Ib	13.4	6,834	1,234	134	1,179	80	0	322	456	1,420	0	27	0	0	965	750	0
						IIa	20.2	6,626	3,515	567	2,424	121	323	425	444	2,141	0	0	81	81	1,656	1,737	0
						IIb	14.0	6,692	1,232	224	1,512	56	0	448	336	2,100	0	0	28	28	1,344	0	0
13	61	F	Hodgkin's disease	4.7	55.0	Ia	105.0	46,200	7,140	1,050	14,070	210	630	3,780	1050	3,360	0	1470	0	0	11 760	14,280	0
						Ib	80.0	29,600	4,000	1,920	6,560	320	480	4,480	640	2,240	0	0	0	160	6,400	23,200	0
						IIa	102.0	39,984	11,016	1,428	13,872	204	1836	3,468	0	1,836	0	204	0	0	6,936	21,216	0
						IIb	60.0	18,960	3,720	480	7,080	0	480	840	480	1,200	0	240	0	0	6 480	20,040	0

TABLE 1.—ABSOLUTE NUMBERS FOR MULTIPLE SAMPLES OF STERNAL MARROW—*Continued*

Case No.	Age	Sex	Diagnosis	Red cell count (millions per c.mm.)	White count of peripheral blood (thousands per c.mm.)	Marrow sample	Total nucleated cell count (thousands per c.mm.)	Neutrophil, mature	Neutrophil bands	Metamyelocytes	Neutrophil myelocytes and premyelocytes	Eosinophilic myelocytes	Myeloblasts	Eosinophils	Monocytes	Lymphocytes	Lymphoblasts	Basophils	Plasma cells	Proerythroblasts	Erythroblasts	Normoblasts	Megaloblasts
14	17	F	Trichinosis	4.1	19.5	Ia	88.0	20,768	21,296	4,752	8,624	4,400	528	8,272	704	6,512	0	528	1408	176	5,280	4,752	0
						Ib	59.2	17,405	12,077	5,446	2,486	2,486	0	6,986	1302	4,026	0	0	237	118	2,368	4,262	0
						IIa	76.0	18,848	12,160	4,560	8,816	4,560	912	8,360	1976	2,432	0	0	152	1216	8,816	3,192	0
						IIb	54.8	18,742	9,206	2,850	4,055	1,754	219	6,466	1315	5,151	0	110	0	219	2,959	1,754	0
15	40	M	Polycythemia vera	7.2	35.6	Ia	102.4	42,598	17,613	3,072	19,866	205	0	819	205	1,024	0	0	0	819	7,373	8,806	0
						Ib	132.4	65,670	24,362	11,916	12,710	265	0	1,854	794	530	0	0	0	0	7,414	6,885	0
						IIa	51.4	29,709	6,579	1,748	5,654	206	0	103	1748	1,439	0	0	0	308	2,364	1,542	0
						IIb	67.4	33,835	11,054	3,505	9,301	404	270	539	809	2,426	0	0	0	404	2,831	2,022	0
16	69	F	Hodgkin's disease	4.0	15.4	Ia	39.2	18,894	5,018	1,254	5,096	392	0	392	1333	2,117	0	0	0	0	3,136	1,568	0
						Ib	43.2	20,218	7,171	2,160	5,357	346	173	518	778	1,987	0	0	0	346	2,333	1,728	86
						IIa	52.6	27,036	7,154	2,314	6,102	316	105	526	947	631	0	0	105	316	4,103	2,946	0
						IIb	46.6	24,698	7,829	1,025	4,753	93	93	559	1398	2,330	0	0	0	0	1,491	2,330	0
17	39	F	Hodgkin's disease	4.0	23.0	Ia	85.0	50,150	9,520	510	17,850	850	340	1,530	170	2,040	0	0	170	0	1,700	170	0
						Ib	107.0	64,200	18,190	428	11,984	642	214	642	856	6,206	0	0	0	214	2,140	1,284	0
						IIa	130.0	65,780	28,600	3,380	17,420	1,040	0	1,040	2080	5,460	0	0	1560	0	2,600	1,040	0
						IIb	96.8	59,629	16,650	1,162	10,648	0	387	774	1355	3,291	0	0	387	0	968	1,549	0
18	60	F	Gangrenous cholecystitis with pernicious anemia	1.8	7.9	Ia	19.8	7,960	1,703	79	2,059	0	0	0	277	1,861	0	0	0	475	2,574	2,297	515
						Ib	6.2	2,480	409	74	744	0	25	12	62	645	0	0	0	112	930	645	62
						IIa	36.6	11,566	2,635	586	5,197	0	73	0	0	3,367	0	0	146	732	6,368	3,953	1976
						IIb	22.8	8,299	1,003	228	2,234	0	137	46	137	2,827	0	0	46	547	4,104	2,508	684
19	51	M	Chronic lymphatic leukemia	3.9	100.0	Ia	128.0	512	512	0	1,024	0	0	0	0	109,312	15,872	0	0	0	768	0	0
						Ib	136.0	3,264	1,360	0	272	0	0	0	0	119,952	10,880	0	0	0	272	0	0
						IIa	120.0	2,976	984	0	0	0	0	0	0	163,968	23,040	0	0	0	1,152	384	0

18	60	F	Gangrenous cholecystitis with pernicious anemia	1.8	7.9	Ia	19.8	7,960	1,703	79	2,059	0	0	0	277	1,861	0	0	0	475	2,574	2,297	515
						Ib	6.2	2,480	409	74	744	0	25	12	62	645	0	0	0	112	930	645	62
						IIa	36.6	11,566	2,635	586	5,197	0	73	0	0	3,367	0	0	146	732	6,368	3,953	1976
						IIb	22.8	8,299	1,003	228	2,234	0	137	46	137	2,827	0	0	46	547	4,104	2,508	684
19	51	M	Chronic lymphatic leukemia	3.9	100.0	Ia	128.0	512	512	0	1,024	0	0	0	0	109,312	15,872	0	0	0	768	0	0
						Ib	136.0	3,264	1,360	0	272	0	0	0	0	119,952	10,880	0	0	0	272	0	0
						IIa	192.0	3,072	384	0	0	0	0	0	0	163,968	23,040	0	0	0	1,152	384	0
						IIb	176.0	4,224	0	0	352	0	0	0	0	151,008	19,712	0	0	0	704	0	0
20	56	M	Asthma	5.0	15.0	Ia	16.6	9,827	1,062	199	1,394	133	33	697	332	2,125	0	0	33	0	398	365	0
						Ib	25.2	10,987	2,218	0	2,470	605	353	1,210	706	3,881	0	0	101	50	1,663	958	0
						IIa	21.3	10,778	1,491	43	1,917	256	0	596	724	3,110	0	85	85	0	1,960	256	0
						IIb	15.2	8,208	1,155	0	1,672	91	0	426	669	1,611	0	61	0	30	1,186	91	0
21	52	M	Pernicious anemia	1.8	6.0	Ia	58.0	13,108	6,844	1,740	4,060	116	0	348	0	2,552	0	0	0	464	13,456	14,152	1160
						Ib	59.4	13,900	7,841	475	3,564	356	0	475	0	3,564	0	0	0	0	15,088	13,662	475
						IIa	30.0	9,960	4,020	240	3,660	120	0	60	180	2,160	0	60	0	0	5,820	3,240	480
						IIb	15.0	4,500	2,130	120	2,340	0	0	90	30	930	0	0	0	30	3,150	1,440	240
22	55	F	Chronic arthritis	4.0	6.3	Ia	33.6	9,274	5,981	538	4,301	202	202	538	134	5,712	0	0	336	134	1,478	4,771	0
						Ib	39.4	9,535	10,008	394	6,383	236	236	473	0	7,722	0	0	79	79	1,576	2,679	0
						IIa	25.8	8,050	4,592	155	4,386	0	206	103	258	3,922	0	0	103	52	1,961	2,012	0
						IIb	27.4	8,439	4,329	110	4,439	0	55	384	55	6,466	0	55	110	0	548	2,411	0
23	42	M	Thrombocytopenic purpura	4.1	4.6	Ia	6.2	2,951	409	12	471	0	0	50	298	1,364	0	0	0	12	285	347	0
						Ib	6.5	2,522	624	0	1,040	0	26	26	182	1,742	0	26	0	0	130	182	0
						IIa	86.0	20,124	13,416	2,408	12,040	0	1204	1,720	172	3,268	0	0	0	516	18,060	13,072	0
						IIb	32.8	7,741	6,954	1,443	4,592	0	328	197	459	2,493	0	0	0	66	2,427	6,101	0
24	22	F	Chronic myelogenous leukemia	3.8	61.0	Ia	176.0	77,088	26,048	7,392	53,504	1,408	3168	2,112	352	1,760	0	352	0	352	1,408	1,056	0
						Ib	144.0	61,344	34,848	6,624	29,088	1,152	2032	1,152	1728	2,304	0	1152	0	0	288	288	0
						IIa	163.0	70,416	35,534	7,498	41,402	1,630	1630	0	652	1,304	0	1956	0	0	326	652	0
						IIb	180.0	85,680	30,240	7,200	45,000	1,440	2160	360	1800	720	0	1080	0	0	3,960	360	0
25	60	M	Carcinoma of prostate with metastases	3.0	13.9	Ia	34.4	15,136	4,816	206	3,027	413	0	1,789	757	3,646	0	206	69	275	3,990	69	0
						Ib	36.4	17,836	4,805	582	2,475	437	0	1,674	0	4,077	0	364	73	364	3,422	291	0
						IIa	51.6	23,323	7,121	722	4,850	516	310	2,993	619	4,438	0	206	206	310	5,366	619	0
						IIb	55.4	22,492	8,864	554	7,645	886	0	2,659	111	3,989	0	111	443	443	6,205	997	0
26	17	M	Schizophrenia	3.6	4.1	Ia	24.4	4,294	2,489	1,513	5,124	439	439	390	683	4,002	0	98	0	146	1,562	3,221	0
						Ib	7.6	2,538	958	15	1,505	0	532	91	0	1,216	0	0	0	0	623	122	0
						IIa	12.4	4,117	1,488	99	2,381	174	124	99	719	1,761	0	25	0	50	744	620	0
						IIb	7.4	3,212	918	163	947	30	89	118	400	1,125	0	0	0	15	266	118	0

8 times its probable error. For each group the deviations were greater from the mean of four counts than of two counts but in no case was the difference statistically significant.

TABLE 2.—THE MEAN AND STANDARD VARIATIONS OF THE TOTAL NUCLEATED CELL COUNT AND NUMBER OF POLYS IN SEVERAL GROUPS OF DISEASES

Group	No. of samples	Mean nucleated white cell count ± P.E	Standard deviation ± P.E.	Mean number of mature polys ± P.E.	S.D. ± P.E.
Blood-forming organs	56	62,588 ± 2292	25,426 ± 1620	22,443 ± 1595	17,696 ± 1128
Locomotor system	8	46,523 ± 5713	23,956 ± 4039	13,238 ± 1571	6,588 ± 1111
Nervous system	12	65,600 ± 8571	44,020 ± 6061	18,553 ± 2495	12,812 ± 1764
Infectious diseases	16	63,688 ± 3331	19,756 ± 2356	15,812 ± 685	4,065 ± 485
Miscellaneous	12	33,508 ± 2392	12,287 ± 1692	14,840 ± 905	4,650 ± 640
Total	104	58,513 ± 2891	43,571 ± 2038	19,388 ± 1095	16,560 ± 774

TABLE 3.—THE STANDARD DEVIATIONS FROM THE MEAN WHITE CELL COUNT OF 2 AND 4 SAMPLES FROM THE SAME PATIENT

Group	Total white cells		Difference ± P.E.	Difference/P.E. diff.
	S.D. ± P.E. (pairs)	S.D. ± P.E. (quartettes)		
Blood-forming organs	9,583 ± 611	11,619 ± 740	−2035 ± 960	2.1
Locomotor system	11,281 ± 1902	18,703 ± 3153	−7422 ± 3683	2.0
Nervous system	22,533 ± 3102	23,503 ± 3236	− 970 ± 4483	0.2
Infectious diseases	14,146 ± 1687	15,957 ± 1903	−1811 ± 2542	0.7
Miscellaneous	3,533 ± 486	6,458 ± 889	−2924 ± 1013	2.9
Total	12,250 ± 573	14,399 ± 673	−2149 ± 884	2.4

TABLE 4.—THE STANDARD DEVIATIONS FROM THE MEAN NUMBER OF POLYS IN 2 AND 4 SAMPLES FROM THE SAME PATIENT

Group	No. of polys.		Difference ± P.E.	Difference/P.E. diff.
	S.D. ± P.E. (pairs)	S.D. ± P.E. (quartettes)		
Blood-forming organs	4570 ± 291	6296 ± 401	−1726 ± 495	3.5
Locomotor system	3487 ± 588	4942 ± 833	−1456 ± 1020	1.4
Nervous system	5152 ± 709	7085 ± 976	−1934 ± 1206	1.6
Infectious diseases	2975 ± 355	3229 ± 385	− 254 ± 524	0.5
Miscellaneous	1490 ± 205	2406 ± 331	− 916 ± 390	2.4
Total	4107 ± 192	5594 ± 262	−1487 ± 325	4.6

Similar deviations for the mean number of polys are given in Table 4 and here, although the variation was less, the indications are not as clear. For the diseases of the blood-forming organs the standard deviation from the mean of two counts from the same sample was 4570 ± 291 polys and for four counts from 2 samples 6290 ± 401 polys, with a difference of −1726 ± 495 which is 3.5 times the probable error and probably not significant. However, for the total 104 counts the standard deviations from the mean of the two counts from the same sample was 4107 ± 192 and from the mean of the four counts 5594 ± 262 and in this case the difference 1487 ± 325 is 4.6 times the probable error or almost certainly significant. In other words, series of four counts from 2 samples taken simultaneously from the same patient may be significantly more variable than two counts from 1 sample in the number of observed polys. Since the number of polys is a factor in the total count and although

two counts from a single sample tend to be more alike than four counts from 2 samples taken simultaneously, sufficient variation was observed in the four counts to lessen considerably the dependence which could be placed on a single quantitative estimate of the number of cells in a single sample. These findings would indicate, therefore, that the validity of quantitative marrow determinations is very questionable. Consequently, it seems inadvisable to continue the use of detailed quantitative data or indices in conjunction with sternal marrow findings.

While demonstrating the fallacies associated with the existent quantitative marrow methods, it is certainly not our intention to belittle, or detract from the importance of sternal puncture or the vital rôle it plays in the establishment of hematologic diagnoses. However, the marrow should be studied just as the pathologist studies a tissue. To facilitate this, the material aspirated by sternal puncture should be centrifuged, and smears made of the buffy coat. Thus a tissue-like preparation is produced which can be studied just like a thin section.

The cellularity of the marrow can be estimated roughly by doing a total nucleated count on the aspirated marrow mixture or by examining the thickness of the buffy coat on the centrifuged specimen. Occasionally doubtful cases arise in which a topographic study of the marrow is necessary to supplement the information derived from sternal puncture. Then a small button of bone can be removed from the sternum by trephine[5] and from this thin sections may be cut. Since this is an actual piece of tissue, quantitative studies of cell types as well as bone marrow histology are permissible. This procedure is much more formidable, however, than sternal puncture, and in most cases qualitative studies as outlined above are adequate. The qualitative study of sternal marrow as advocated here naturally precludes laboratory technicians doing anything but the preparation and staining of the smears, and the total cell counts. Examination of the stained marrow preparations requires the attention of an experienced hematologist, whose judgment must naturally be tempered by a thorough clinical examination of the patient.

Conclusions.—1. A quantitative study of a series of multiple sternal marrow samples was undertaken.

2. Statistical analysis indicates that quantitative determinations on aspirated marrow samples are inaccurate.

3. Qualitative marrow studies are invaluable in establishing hematologic diagnoses.

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THE SURVIVAL AFTER TRANSFUSION OF HUMAN ERYTHROCYTES THAT HAVE BEEN STORED IN CITRATE–GLUCOSE

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In previous reports we described our observations on the keeping qualities of citrated human blood stored at 4° to 6° C.,[2] the survival after transfusion of red cells so stored,[3] and the keeping qualities of citrated human blood to which glucose has been added.[4] The present report,* the fourth and last of the series, describes the survival, after transfusion, of red blood cells preserved with the aid of glucose.

Method. Blood was collected in 20% dihydric sodium citrate to make a final concentration of 0.4%, and glucose, 5.4% in water, was added in quantity equal to half the volume of blood. Flasks were kept undisturbed at 4° to 6° C. The life span of the erythrocytes after entering the recipients' circulation was determined by a modification of Ashby's method of non-agglutinable cell counts, as in our previous study.

Chart 1 shows the individual survival curves of 12 bloods. The numbers at the end of the curves indicate the days each blood was stored prior to use. The amount of the transfusions was 500 cc. (glucose not counted) with 2 exceptions of 750 cc. and 1000 cc.

In Chart 2 the data of the present study and that of the former study on the survival of red cells of citrated blood (containing no glucose) have been combined for the sake of contrast. Citrated cells are represented by the block at the left of the graph, the cells preserved by glucose the block on the right. The chart is constructed by plotting for each blood the number of storage days against the days of cell survival in the recipient. This chart shows that erythrocytes preserved with the aid of glucose remained useful to the recipient after a much larger storage period than cells simply citrated. In other words, cells stored in glucose for about 14 days survived

* The authors offer apologies for not presenting a greater number of observations. Such data are difficult to collect, and recent loss of personnel has made it impossible to carry the study further. The data, however, are adequate to demonstrate the prolonged survival of red blood cells preserved with glucose.

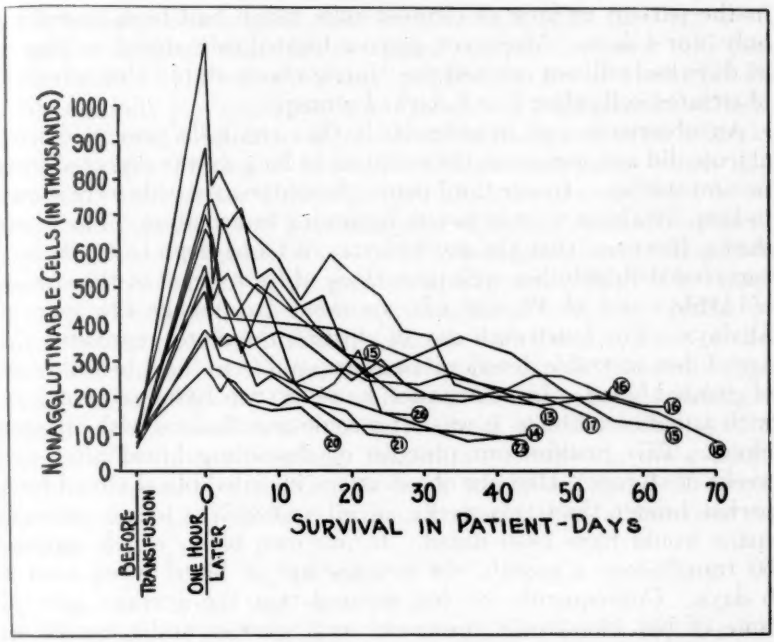

CHART 1.—Erythrocyte survival after transfusion of blood stored in citrate-glucose.

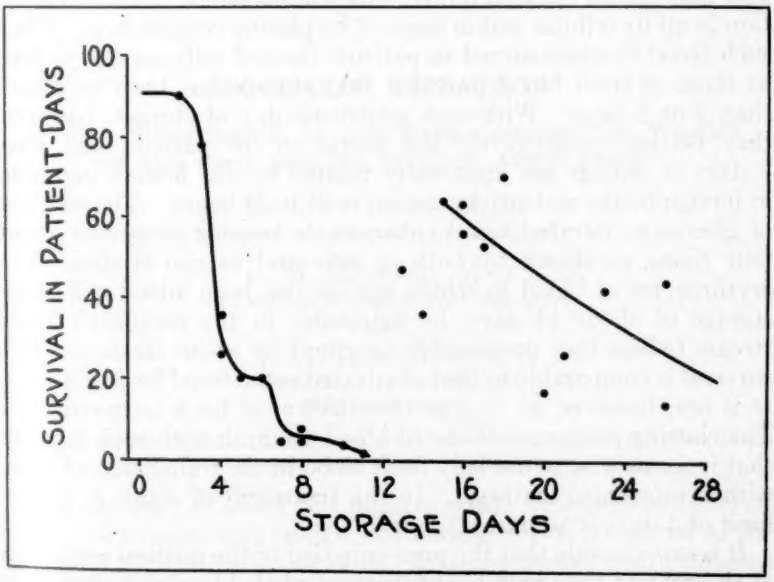

CHART 2.—Relation between storage time and survival of erythrocytes after transfusion. The observations on the left of the chart refer to citrated blood, those on the right of the chart to blood stored in citrate-glucose.

in the patient as long as citrated cells which had been stored for only 3 or 4 days. Moreover, glucose treated cells stored as long as 26 days had still not reached the "foreign body state" characteristic of citrated cells after 7 or 8 days of storage.

An observation of importance is that red cells preserved with glucose did not survive in the recipient as long as was expected from *in vitro* studies. In our third paper glucose treated cells were shown to keep for about 4 weeks before beginning to hemolyze. The graph shows, however, that the erythrocytes of blood kept 13 to 18 days survived definitely less well than those of fresh blood in the studies of Ashby[1] and of Wearn[6] who recorded an average life span of 81 days. The fourteenth day of storage, therefore, represents the age of demonstrable deterioration, comparable to the 3 to 4 day age of citrated blood. In no instance, however, was harmless hemolysis with jaundice noted as it was after some transfusions with citrated blood. This justifies our practice of discarding blood after two weeks of storage. Had our observations included blood stored for a period briefer than two weeks, in all probability longer survival spans would have been noted. In our own bank, which supplies 50 transfusions a month, the average age of blood when used is 6 days. Consequently we feel assured that the average survival time of red blood cells preserved with glucose under conditions comparable to those in our institution is better than 50 days.

General Summary. Summarizing this entire study, it may be said that chilled citrated human blood undergoes a rapid deterioration in all its cellular and in some of its plasma components. When such blood is administered to patients the red cells survive as long as those of fresh blood provided that storage has been no longer than 2 or 3 days. With each additional day of storage, however, they become progressively less useful to the patient, and after 7 days of storage are apparently treated by the human organism as foreign bodies and are eliminated in 24 to 48 hours. The addition of glucose to citrated blood enhances its keeping properties about four times, as shown by both *in vitro* and *in vivo* studies. The erythrocytes of blood to which glucose has been added will, after storage of about 14 days, be detectable in the recipient's blood stream (where they presumably function) for about 50 days. This survival is comparable to that of citrated cells stored for 3 or 4 days. It is not, however, as long as the survival of fresh unstored cells. The clotting properties of stored blood diminish with such rapidity that it seems wise to use only fresh blood in the transfusion of those with hemorrhagic diathesis. In the treatment of sepsis a storage limit of 5 days is advisable.[5]

It seems possible that the preoccupation of the medical profession at the present time with banks, both of whole blood and of plasma, has led us to forget that fresh whole blood is easily obtainable, and that it has distinct advantages over any substitute. The blood

bank, in fact, necessitates some compromises with the very best technique of blood transfusion. These compromises are: the use of the universal donor for many patients, a practice which has resulted fatally in a small per cent of cases; the use (usually) of non-fasting donors, a practice of considerable danger to food allergic recipients; the filtering of blood, usually through gauze which imparts lint; and the use of blood which has undergone at least some deterioration in cells and in components of the plasma. We realize, of course, that the bank offers certain advantages to be set off against these objections, namely, the greater rapidity with which blood may be supplied in emergencies; the performance of tests for syphilis by skilled rather than by unskilled workers; and the avoidance of the confusion and inconvenience incident to the selecting of individual donors of fresh blood. On the whole, in routine practice in larger hospitals where blood is not stored too long, the blood bank would seem to offer more advantages than disadvantages to the average patient. Recourse, however, to fresh whole unfiltered blood of homologous type from fasting donors should still be practised in selected cases.

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BLOOD CLOT RETRACTION

II. The Significance of the Extracorpuscular Volume of the Clot and its Clinical Application*

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The efficiency of blood clot retraction may be measured in terms of the extracorpuscular volume of the clot.[1] This is defined as the volume of the clot exclusive of its contained packed cells expressed as a percentage of the total volume of the specimen studied.

* Aided by a grant from the Christine Breon Fund and by a grant from Mr. Frank Kennedy.

Method. The upper end of a copper wire about 1 mm. in diameter is attached to a cork. The free end of the wire is bent in the shape of a hook. An arbitrary amount of venous blood, usually 5 cc., is carefully transferred to a graduated centrifuge tube and the cork and wire are fitted so that the hook is immersed in the upper layers of the specimen. After coagulation of the blood has occurred, the tube is placed in a water-bath (37° C.) for 1 hour. It is then taken from the bath and the total volume of the specimen is recorded. The clot is elevated, allowed to drain, and then removed. The clot volume is measured by subtracting the residual volume of serum from the total volume of the specimen. To obtain the volume % of the blood clot, the observed volume of the clot is divided by the total volume of the specimen and the quotient is multiplied by 100. The packed cell volume including all cellular elements is obtained by centrifugalization of the blood at 3000 r.p.m. for 30 minutes. The difference between the total packed cell volume in % and the clot volume in % is a measure of the *extracorpuscular volume of the clot.*

The authors[1] found that in 100 normal subjects the extracorpuscular mean volume measured 9.1% and the standard deviation of the sample was 7.5%; in 42 subjects who had prothrombin concentrations of 50% or less, the mean value was 18.2%, and the standard deviation was 12.4%; and in 35 subjects who had platelet counts of 200,000 or less the mean value was 38.9% and the standard deviation was 14.1%. The normal value was arbitrarily considered to fall within two standard deviations of the mean (−5.9% to 24.1%). Using this criterion, blood clot retraction was diminished in 13 of the 42 patients who had hypoprothrombinemia and in 30 of the 35 patients who had thrombocytopenia. In some patients with hypoprothrombinemia or thrombocytopenia, the blood clot may retract normally, and conversely deficient clot retraction may be observed in some patients whose platelet counts and prothrombin concentrations are normal. Furthermore, deficient clot retraction may be found in patients who do not have abnormal bleeding, while normally retracting clots are frequently seen in those who suffer from marked bleeding tendencies.

The measurement of blood clot retraction alone does not give sufficient information regarding the hemostatic equilibrium to permit any final conclusions concerning the tendency to bleed. The interpretation of the clinical significance of deficient clot retraction can be made only in the light of other hemostatic tests. Normal values for these tests are given in Table 1.

The following cases demonstrate the application of blood clot retraction measurements when considered in relation to other hemostatic tests in the study of the problem of abnormal bleeding. Cases 1 to 4 illustrate the frequent association of hypoprothrombinemia and thrombocytopenia with deficient blood clot retraction. Cases 5 and 6 demonstrate some aspects of the problem presented by the finding of deficient clot retraction in patients with normal prothrombin concentrations and normal platelet counts. Although a careful study of each patient was undertaken, only the pertinent data of each case is here recorded.

TABLE 1.—THE NORMAL VALUES FOR HEMOSTATIC TESTS

Test	Mean	2 standard deviations (σ_x)	Range
Bleeding time (Ivy) in minutes	3.2	1.4	0.4 to 6.0
Coagulation time (modified Lee and White) in minutes	8.8	2.7	3.4 to 14.2
Platelet count (Rees and Ecker) per c.mm.	422,000	87,000	248,000 to 596,000
Extracorpuscular volume of clot, %	9.1	7.5	(−)5.9 to 24.1
Prothrombin concentration (Quick) in %	...	...	70 to 100
Capillary permeability (Dalldorf), number of petechiæ with 200 mm. Hg vacuum pressure	...	...	0 to 10

The standard statistical method was used in setting up the limits of normality for the bleeding time, coagulation time, extracorpuscular volume of the clot and platelet count. One hundred normal subjects were studied. The limits of significance of the data were arbitrarily set at two standard deviations from the mean, which includes approximately 96% of the observations. The mean is taken at the point of reference. All measures which were calculated were at least 3 times their sampling errors. The limits of normality for the prothrombin concentration and capillary permeability were arbitrarily set by direct observation. The range of the prothrombin concentration was from 65% to 100%; 98% of the observations fell between 70% and 100%. The range of the capillary permeability was from 0 to over 30 petechiæ. There were not more than 10 petechiæ in 88% of the observations.

CASE 1. Y. S. White woman, aged 19. *Diagnosis:* idiopathic thrombocytopenic purpura.

Clinical Summary. The patient had suffered from menorrhagia from the time of menarche (aged 13) until her 17th year of age. She had had recurrent ecchymoses since her first menstrual period. The occurrence of frequent epistaxis during the past 2 years had recently been controlled by a submucous resection. She had suffered from symptoms of hypothyroidism for the past year. The spleen was not palpable. B.M.R. was −11%. Plasma cholesterol 123 mg.%. Plasma cevitamic acid 1.71 mg.%. The results of the hemostatic tests were as follows:

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiæ)	Remarks
9/28/39	>30	6	75	46	75	Shower	Thyroid, 1 gr. daily. Hypothyroidism corrected, but ecchymoses continue. Moccasin snake venom therapy from 10/31/39 to 7/26/40 without significant effect. Ecchymoses continue.
10/ 6/39	>30	8½	90	52	95	Shower	
10/20/39	>30	6½	100	50	60	Shower	
10/31/39	>30	6	75	53	70	Shower	
11/ 3/39	>30	8	85	60	95	Shower	
12/ 4/39	>30	7	75	60	100	Shower	
3/ 9/40	>30	11½	100	43	110	28	
3/21/41	>30	11½	100	44	110	Shower	

The results of the hemostatic tests performed on this patient illustrate the characteristic findings associated with thrombocytopenia. The bleeding time was prolonged, the coagulation time and prothrombin concentration were normal, the capillary permeability and the extracorpuscular volume % of the clot were markedly increased.

CASE 2. L. D. White girl, aged 12. *Diagnosis:* dysovarian purpura.

Clinical Summary. The patient had experienced the onset of petechiæ and purpuric maculæ 4 days before hospitalization. The spleen was not palpable.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiæ)	Remarks
1/ 8/41	>30	10	80	31	70	6	Body covered with petechiæ and purpuric maculæ.
2/24/41	7	7	90	12	450	No	All petechiæ and purpuric spots disappeared with 1st menstrual period 2 weeks after first observation.
3/20/41	3½	10	95	18	490	2	No further bleeding.

The results of the hemostatic tests demonstrate a diminution in the bleeding time and in the extracorpuscular volume of the clot coinciding with recovery from thrombocytopenia.

CASE 3. M. F. White man, aged 55. *Diagnosis:* portal cirrhosis of the liver.

Clinical Summary. Two months before our observation the patient noted the onset of ascites, slight jaundice, fatigue and loss of weight. He had also had frequent severe epistaxis for a period of 2 weeks. The liver was enlarged 4 cm. below the right costal margin. The spleen was not palpable. The rose bengal test showed marked impairment of biliary excretory function (8 minutes 100%, 16 minutes 90%). Serum proteins: total 8%, albumin 1.46%, globulin 6.54%. Plasma cevitamic acid, 1.4 mg.%. Plasma fibrinogen 0.22%.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiæ)	Remarks
3/26/40	4½	6	30	34	360	No	Recurrent epistaxis.
4/ 1/40	6	5½	30	40	180	No	5 mg. 5-amino-2-methyl naphthol HCl intravenously.
4/ 2/40	5½	7½	30	45	270	No	Condition unchanged.
4/ 3/40	5	8	30	52	210	No	Epistaxis continues.

The results of the hemostatic tests in this case demonstrate the association of impaired clot retraction with hypoprothrombinemia in a patient suffering from advanced cirrhosis of the liver. The administration of vitamin K failed to alter either the hypoprothrombinemia or the extracorpuscular volume of the clot.

CASE 4. M. M. White woman, aged 65. *Diagnosis:* cholangeitis with partial obstructive jaundice, multiple pyogenic abscesses of the liver.

Clinical Summary. During the 3 weeks preceding our observation the patient had suffered from right upper abdominal pain, slight jaundice, intermittent fever, dark colored urine and light colored stools. For 1 day she had had recurrent profuse epistaxis, which could not be controlled by repeated nasal packs. Icterus index 75. Plasma fibrinogen 0.87%.

Date	Bleed time (min.)	Coag. time (min.)	Prothr. concentr. (%)	Extracorp. vol. of clot (%)	Platelet count (thous. per c.mm.)	Capil. permeability (petechiæ)	Remarks
9 A.M. 3/3/40	7½	18	3	38	380	No	Profuse epistaxis. Given 5 mg. 4-amino-2-methyl naphthol hydrochloride I.V.
5 P.M. 3/ 3/40	1	6	30	28	—	No	Epistaxis stopped and nasal packs were removed 1 hour after vitamin K.
9 A.M. 3/ 4/40	1	4½	75	18	—	No	No further epistaxis. Died 1 hour later.

The results of the hemostatic tests in this case demonstrate improvement in clot retraction coinciding with a remarkable elevation of the prothrombin concentration following the administration of vitamin K.

CASE 5. A. M. White woman, aged 19. *Diagnosis:* thrombocytopenic purpura.

Clinical Summary. The patient was first seen on January 25, 1939, with complaints of marked gingival bleeding, epistaxis, ecchymotic areas on the buccal mucosa and pharynx, purpuric spots in the conjunctivæ, petechial hemorrhages scattered over the body and splinter hemorrhages under the nails of the fingers and toes of 1 months' duration. The spleen was palpable 2 finger breadths below the left costal margin. Bleeding time (Duke), greater than 20 minutes. Platelet count (Rees and Ecker) 80,000 per c.mm. Capillary permeability (Dalldorf) markedly increased. Plasma vitamin C 0.48 mg.%. During 1 week of hospitalization, she was started on a course of moccasin venom therapy, her symptoms gradually abated, and her spleen became impalpable. The platelet count varied between 80,000 and 120,000 per c.mm. She remained almost asymptomatic for 10 days, then suffered a recurrence of purpuric manifestations, including menorrhagia. At this time her platelet count was 80,000. During the following 3 weeks she was given Roentgen therapy to the spleen (total of 1200 r to each of 3 areas), all of her purpuric symptoms disappeared and her platelet count rose to 300,000 per c.mm. She had no symptoms of purpura for the next 6 months. In September and October, 1939, she noted on several occasions, small areas of petechial hemorrhages, and during these months her platelet count varied between 180,000 and 260,000 per c.mm. Since that time she has been entirely free of purpura and her platelet counts have varied between 290,000 and 400,000 per c.mm.

Unfortunately blood clot retraction measurements were not done until the patient was recalled specifically for this purpose in September, 1941. The results of the hemostatic tests were as follows:

Date	Bleeding time (min.)	Coagulation time (min.)	Prothrombin concentration (%)	Extracorpuscular vol. of clot (%)	Platelet count (thous. per c.mm.)	Capillary permeability (petechiæ)
9/17/41	4	7	70	29	320	No
9/27/41	3	9½	70	34	360	No

Because of the previous thrombocytopenia, it might be assumed that the deficient clot retraction observed in the blood of this patient was due to a defective clot retractive function of the platelets, since poor clot retraction persists despite an elevation of the platelet count to normal numbers. The assumption of "thrombasthenia" in this patient is strengthened by the recent occurrence of thrombocytopenia in her sister, who has suffered from petechial hemorrhages, ecchymoses, gingival bleeding, and menorrhagia for the past five months. In the latter, the bleeding time has varied between 14½ and over 30 minutes, the coagulation time between 8 and 12½ minutes, the prothrombin concentration between 65% and 100%, the extracorpuscular volume of the clot between 16% and 49%, and the platelet count between 80,000 and 190,000 per c.mm. The capillary permeability has been increased on all occasions.

CASE 6. J. F. Male, aged 29. *Diagnosis:* atypical thrombocytopenic purpura.

Clinical Summary. The patient had bruised easily and had suffered from frequent epistaxis since childhood. For the past year the epistaxes had increased in frequency, fresh blood had been noted in the stool on many occasions, and there had been recurrent showers of large petechial hemorrhages over his lower extremities. Epistaxis had been intractible for the past month. An indolent ulcer had been present over his left tibia for the

past 10 years. Nine years previously, after the third of a series of salvarsan injections, which had been given in an attempt to heal the ulcer, he had developed toxic hepatitis, which had persisted for 4 months. The family history was negative except that the father had had frequent epistaxis. On entry to the hospital the patient was found to have generalized purpura, most marked on the lower extremities. There were many bleeding points on Kiesselbach's area in the right nostril. The oral and pharyngeal mucous membranes were spotted with many small hemorrhages. Prolapsed bleeding hemorrhoids were present. The spleen was palpable 2 fingerbreadths below the left costal margin on deep inspiration. There were many red blood corpuscles in the urine. Plasma fibrinogen 1.17%. Serum calcium 9.8 mg.%.

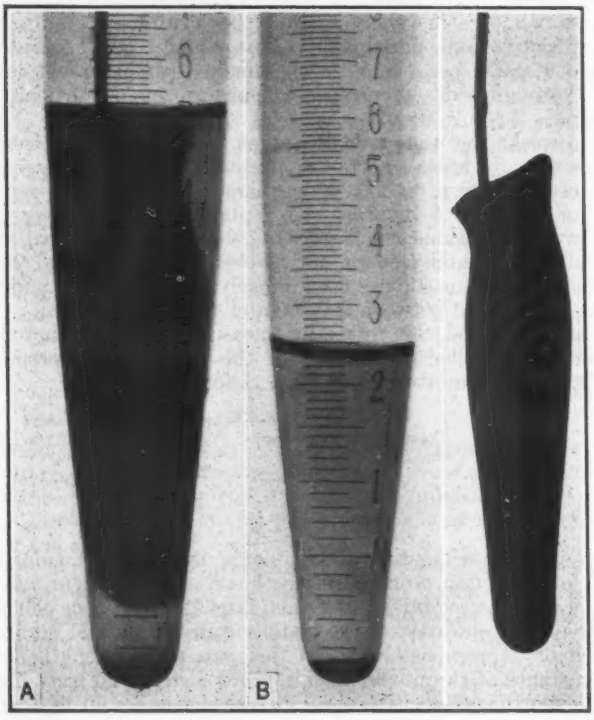

FIG. 1.—The appearance of the blood clot in a normal subject. Prothrombin concentration 100%. Platelet count 480,000 per c.mm. Serum volume 43%. Clot volume 57%. Packed cell volume 39. Extracorpuscular volume of clot 18%. While this clot is within normal limits for a patient with this packed cell volume, it would be quite abnormal if the packed cell volume were 16 as in Figure 2. In that case the extracorpuscular volume of the clot would be 41%.

While in the hospital, the patient bled into the right maxillary sinus, into the tissues of the neck, and under the right parietal pleura. He died on January 8, 1942, and at autopsy there was found bilateral cavernous sinus thrombosis and subarachnoid hemorrhages.*

* Further details regarding the coagulation defect and autopsy findings in this patient will be published at a later date.

The results of the hemostatic tests were as follows:

Date	Bleeding time (min.)	Coagulation time (min.)	Prothrombin concentration (%)	Extracorpuscular vol. of clot (%)	Platelet count (thous. per c.mm.)	Capillary permeability (petechiæ)
12/ 5/41	>30	24	75	51	70	Shower
12/24/41	10½	42	40	44	160	2
12/30/41*	>30	105	45	43	230	4
1/ 2/42	>30	175	70	43	250	No
1/ 6/42	>30	130	80	44	180	10

* 2 mg. Synkamin (4-amino-2-methyl-naphthol) were given daily by the intravenous route.†

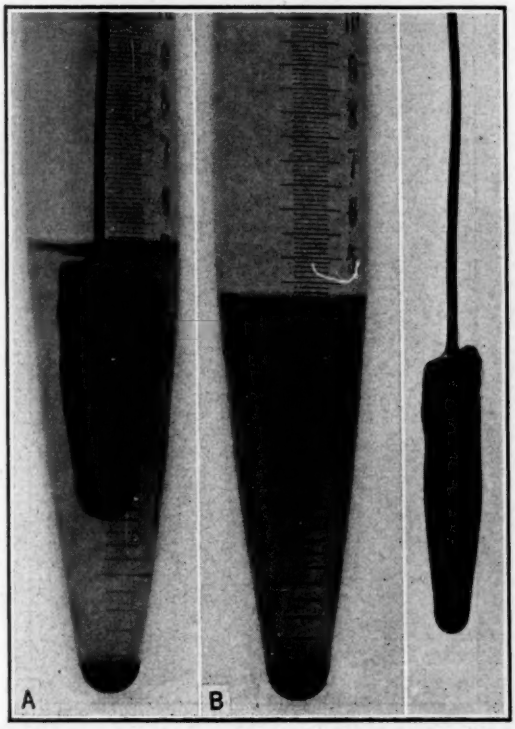

FIG. 2.—Normal clot retraction in a patient with pernicious anemia. Prothrombin concentration 65%. Platelet count 400,000 per c.mm. Serum volume 80%. Clot volume 20%. Packed cell volume 16. Extracorpuscular volume of clot 4%.

Between December 9 and December 20, 1941, the patient was given Roentgen therapy to the spleen (a total of 1200 r to each of 2 areas). During the following 3 weeks daily platelet counts varied between 120,000 and 250,000. Despite the elevation of the platelet count to the lower limits of normal, the degree of clot retraction remained unchanged and the coagulation time continued to be markedly prolonged. It was observed on the blood smear that the platelets were large, darkly staining and did not contain any granules.

Regardless of their numbers, the platelets in this patient were deficient both in their clot retractive function and in their ability to supply thromboplastin for the processes of coagulation of the blood.

† Kindly furnished by Parke, Davis & Company, Detroit, Mich.

Discussion. The blood clot is made up of cells, a fibrin meshwork and serum. The extracorpuscular volume of the clot is composed chiefly of serum occluded within the clot. The packed cell volume must be known in order to calculate the extracorpuscular volume of the clot. The appearance of normal clot retraction in a subject whose packed cell volume was 39 is shown in Figure 1, and of normal clot retraction in a patient whose packed cell volume was 16 in

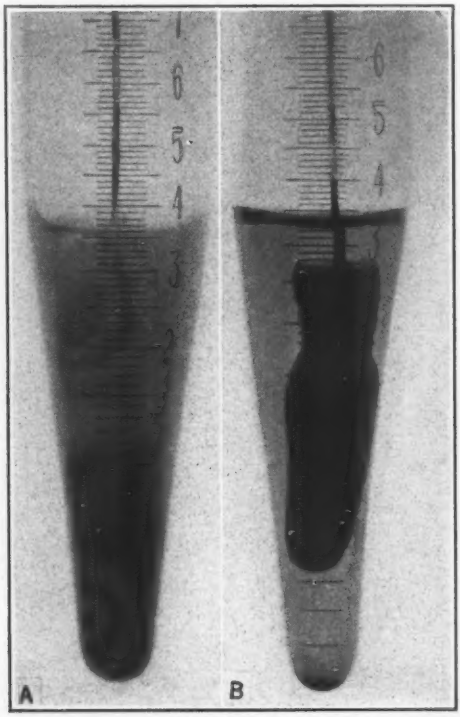

FIG. 3.—The appearance of the blood clot in a patient with obstructive jaundice. *A*, With hypoprothrombinemia—prothrombin concentration 10%. Serum volume 35%. Clot volume 65%. Packed cell volume 14. Extracorpuscular volume of clot 51%. *B*, The clot of the same patient after correction of hypoprothrombinemia following the administration of vitamin K. Prothrombin concentration 90%. Serum volume 72%. Clot volume 28%. Packed cell volume 13. Extracorpuscular volume of clot 15%.

Figure 2. While clot retraction in both of these patients was within normal limits for the respective packed cell volumes, it should be noted that had the volume of the clot in the second patient been the same as that observed in the first, the extracorpuscular volume would have been 41% rather than 4% and decidedly pathological. The appearance of deficient clot retraction in a patient with hypoprothrombinemia due to obstructive jaundice before the administration of vitamin K is shown in Figure 3*A*, and of normal clot

retraction in the same patient after its administration in Figure 3*B*. Markedly deficient retraction of the clot of a patient with thrombocytopenia is shown in Figure 4.

In addition to the volume of the packed cells and the quantity and quality of the prothrombin and platelets, it is conceivable that clot retraction may be influenced either by fibrinogenopenia, an extremely rare condition, or by the inability of the formed fibrin

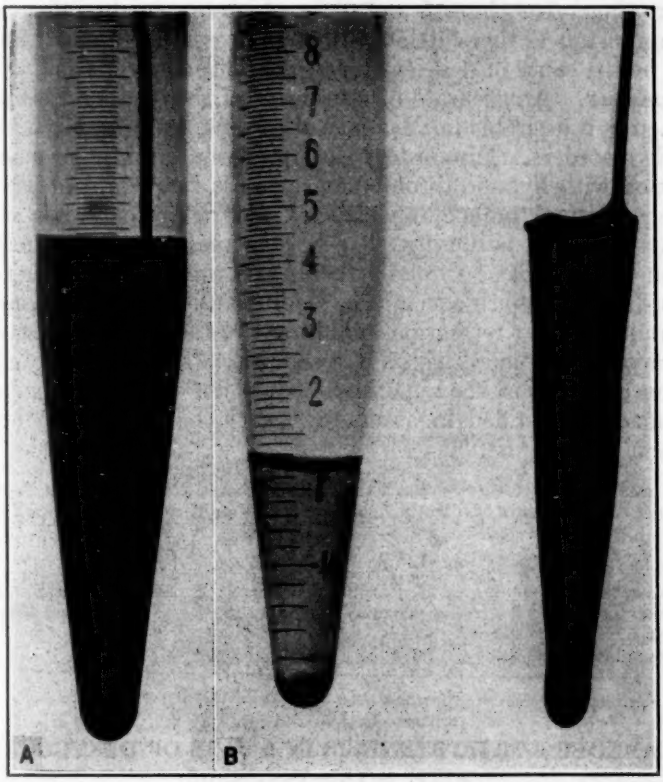

FIG. 4.—The appearance of the blood clot in a patient with thrombocytopenia (aplastic anemia). Prothrombin concentration 60%. Platelet count 70,000 per c.mm. Serum volume 24%. Clot volume 76%. Packed cell volume 26. Extracorpuscular volume of clot 50%.

to behave in the normal manner. The latter condition might be called "fibrinasthenia." However, there would be no way to prove the existence of such a disorder. In addition, it has been shown that blood clot retraction may be profoundly influenced *in vitro* by the addition of various amino acids.[2] Hence, there may be metabolic defects resulting in excesses in the blood stream of substances which promote or inhibit clot retraction. It may be that deficient clot retraction is due in some instances to what has been termed

"thrombasthenia" (Glanzmann), a condition in which the platelets although present in normal numbers are said to be deficient in their clot retracting ability. It would be difficult to prove or disprove the existence of such a condition. Some information could perhaps be obtained by *in vitro* experiments with isolated platelets. Certainly it must be conceded that the finding of deficient blood clot retraction in the presence of a normal platelet count does not prove the existence of "thrombasthenia." We have made some clinical observations (see Cases 5 and 6) in which one might infer that in certain instances the platelets, although present in normal numbers, may be the cause of deficient blood clot retraction.

Summary. An accurate measurement of the degree of blood clot retraction is desirable in the study of patients suffering from hemorrhagic disorders. Diminished clot retraction is often seen in conjunction with hypoprothrombinemia and is frequently observed in patients with thrombocytopenia. It may be present when neither of these conditions obtains. One cannot assume under the latter circumstances that "thrombasthenia" is present, as other conditions, including fibrinogenopenia, "fibrinasthenia" or the presence of circulating clot retraction-inhibiting substances, may likewise be responsible for diminished clot retraction. There is some clinical evidence to support the hypothesis that under certain circumstances one may be justified in assuming that a condition of "thrombasthenia" may exist.

We take this opportunity to thank the staff members of the Division of Pediatrics, University of California Medical School for permission to report the data on Case 2.

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CALCAREOUS AORTIC STENOSIS IN A CASE OF DEXTROCARDIA WITH SITUS INVERSUS

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Transposition of the viscera is an uncommon condition. LeWald[3] recorded its clinical incidence as 1 in 35,000 physical examinations of recruits for the U. S. Army. Considerably more infrequent, however, is the association of congenital dextrocardia with acquired lesions of the cardiovascular system.

In 1911 Owen[5] reported a case of situs inversus in which mitral stenosis involved the transposed heart. Willius[6] in 1931 described

dextrocardia with situs inversus complicated by hypertensive heart disease. The electrocardiogram in the latter case showed changes indicative of strain of the left ventricle. In 1938 Crawford and Warren[1] reported dextrocardia with situs inversus associated with coronary thrombosis. Electrocardiographic studies revealed an infarct in the posterior wall of the left ventricle. In the same year Manchester and White[4] recorded transposition of the viscera complicated by hypertensive and coronary heart disease. The electrocardiogram showed changes compatible with myocardial disease. More recently, King[2] has described the association of situs inversus with syphilitic aortitis and aortic insufficiency.

The purpose of this paper is to present a case of congenital dextrocardia complicated by calcareous aortic stenosis which, as far as can be ascertained, has not been previously recorded.

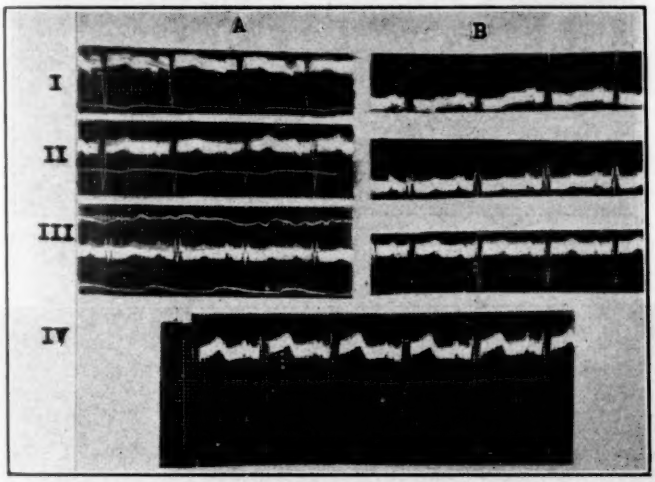

FIG. 1.—*A*, Routine Leads I, II, III, IV; *B*, with electrodes reversed in the limb leads to correct for the dextrocardia.

Case Report. G. J., a 43-year-old Swedish merchant seaman, was admitted to the hospital on September 15, 1941, because of nocturnal dyspnea and cough of 1 week's duration. He had been well until 3 weeks prior to entry when he experienced marked dyspnea on exertion and aching pain in the right mammary region. Edema of the ankles became evident shortly after the onset of symptoms. From the age of 15 he engaged in laborious occupations without limitation of activities. He stated that he had had a serious lung or heart ailment in 1907 and gonorrheal urethritis in 1938. There was no history of syphilis or rheumatic fever.

Examination revealed a well-nourished and well-developed adult white male who was dyspneic, orthopneic and cyanotic. There was a linear birthmark in the midline of the forehead. The veins in the neck were prominent and pulsating. Temperature was 99.4° F, pulse 96, respirations 30. The radial pulses were of small volume, equal and regular. The blood pressure was 110/85. The apex impulse of the heart was felt in the sixth right intercostal space in the anterior axillary line. There was a marked systolic thrill

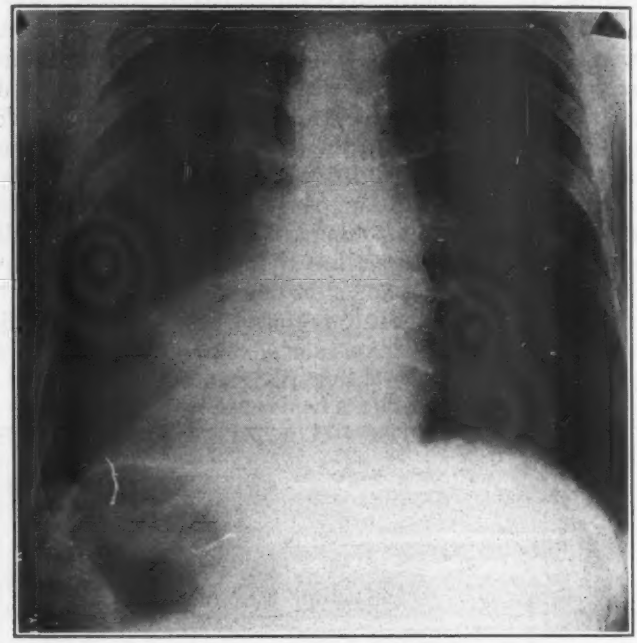

FIG. 2.—Roentgenogram showing dextrocardia with marked enlargement of the heart. "Gas bubble" in stomach is seen on right side.

FIG. 3.—Roentgenogram, lateral view, showing calcification in the aortic valve.

in the second and third intercostal spaces to the left of the sternum. A loud harsh systolic murmur was heard with maximal intensity in this area and to a lesser degree over the entire precordium and neck vessels. The aortic second sound was absent and replaced by a short faint diastolic murmur. There was dullness at both lung bases posteriorly, with moist râles throughout the lower lobes. The liver was situated on the left side, its border being palpable 3 fingerbreadths below the costal margin. The spleen was not felt. There was marked edema of the lower extremities.

The blood Wassermann and Kahn reactions were negative.

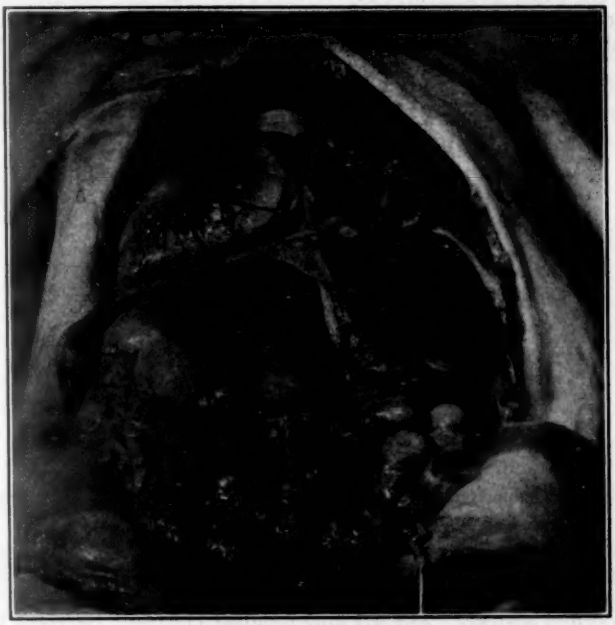

FIG. 4.—Dextrocardia with situs inversus.

Electrocardiogram (Fig. 1*A*) shows normal rhythm with a ventricular rate of 90; P and QRS waves inverted in Lead I; T waves upright in all leads and slight elevation of the S–T segment in Lead I; P–R interval 0.15 sec., QRS interval .07 sec.; marked right axis deviation.

A roentgenogram of the chest reveals the maximum heart measurements as 10.8 cm. to the right and 7 cm. to the left, the transverse diameter of the chest being 28.4 cm. The lateral view shows a dense shadow in the region of the aortic valve suggestive of calcification.

Fluoroscopic examination with the aid of barium taken by mouth demonstrated complete situs inversus viscerum.

Following bed rest and digitalization the condition of the patient improved until October 28, when there was a sudden onset of knifelike pain in the lower left chest with elevation of temperature to 101° F. Expectoration of bloody sputum developed on the following day. Roentgen ray of the chest revealed evidence of an infarct at the base of the left lung. Dyspnea increased and necessitated the use of an oxygen tent. Mild icterus developed. Subsequent chest films showed multiple infarcts throughout both lungs. Patient failed to respond to therapy and died on December 20.

Postmortem Examination. There was complete transposition of all the thoracic and abdominal viscera. The parietal epicardium was smooth and glistening. The visceral epicardium presented large plaques of milky discoloration and thickening. The heart (wt. 810 gm.) was markedly enlarged downward and to the right. The right auricle was moderately dilated and its wall was thin. Upon opening the chambers of the heart the mural endocardium appeared ordinary. The foramen ovale was closed. The mitral, tricuspid, and pulmonary valves showed no lesions and their orifices were of normal size. The aortic orifice showed marked stenosis and admitted an instrument 1 cm. in diameter with difficulty. The aortic cusps were fused and completely replaced by spikelike calcareous masses. The aortic ring showed slight thickening with focal deposits of calcareous material. The left ventricle averaged 25 mm. in thickness, and the right 6 mm. There was great hypertrophy of the papillary muscles. The aorta

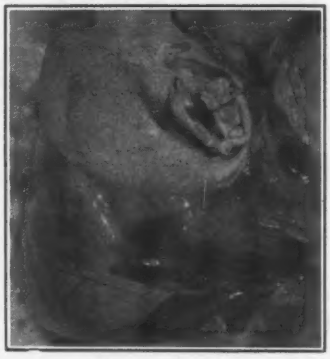

FIG. 5.—Calcareous stenosis of the aortic valve in "mirror image" dextrocardia.

was of slightly smaller caliber than normal. Its wall was thin and elastic and revealed no significant pathologic changes. The arteries arising from the aorta, as well as those throughout the body, showed complete reversal of their normal position. The left lung weighed 1120 gm., the right 1000 gm. There were 3 lobes in the left lung and 2 in the right. Numerous large infarcts were present throughout both lungs. On section old and recent infarcted areas were noted. The intervening parenchyma was waterlogged. The liver presented an advanced nutmeg appearance.

The cardiac findings were compatible with a rheumatic etiology.

Discussion. The diagnosis of situs inversus was made on the basis of physical findings, the visualization of the transposed heart, stomach and liver by Roentgen ray, and the inversion of the P waves in Lead I of the electrocardiogram.

Stenosis of the aortic valve was recognized from the classical signs of systolic thrill and murmur in the aortic area (in this case the second left interspace), absent second aortic sound, narrow pulse pressure and small pulse. The configuration of the heart and the demonstration of calcification in the region of the aortic valve on the roentgenogram supported this impression.

The electrocardiograms are of interest since they differ from those obtained in uncomplicated situs inversus. In the latter there is

total inversion of Lead I and transposition of Leads II and III. When the electrodes in the limb leads are reversed to correct for the dextrocardia, a normal electrocardiogram is obtained. In this case, however, the effect of the acquired valvular lesion was superimposed upon that of the congenital anomaly. Thus there is unusually marked right axis deviation, slight elevation of the S–T segment in Lead I and upright T wave in Lead I. With reversal of the electrodes, one observes left axis deviation and slight depression of the S–T segment with inversion of the T wave in Lead I, a record indicative of strain of the left ventricle (Fig. 1*B*).

Summary. A case is presented in which calcareous aortic stenosis (rheumatic?) was found in a 43-year-old male with situs inversus. Electrocardiograms showed the effect of the conditions cited. We have found no similar case reported.

The authors wish to acknowledge the assistance of Dr. J. G. Pasternack who performed the postmortem examination.

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METABOLIC STUDIES ON NEOPLASM OF BONE WITH THE AID OF RADIOACTIVE STRONTIUM*

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Chemical and spectrographic studies regarding the mineral composition of the animal body have revealed the presence of "trace" amounts of strontium in living tissue. Stoeltzner[9] has reported the first description of this by König in 1874 and her own experiment of feeding dogs with strontium. She found a selective uptake in the spongiosa and in the epiphyseal regions of the bones. Growing animals which were maintained on a diet low in calcium and in which the normal calcium requirement was replaced by strontium devel-

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oped toxic symptoms clinically resembling rickets. The strontium-fed animals showed a considerably higher amount of water-soluble alkaline earth content in the bones than is found in rickets, and therefore a biochemical difference between the two elements was apparently demonstrated. Lehnerdt[4] found that a part of ingested strontium was excreted in the milk. He also found a considerable amount in the bones of suckling young. According to McCollum,[5] Wheeler (loc. cit.) found that strontium was capable of replacing calcium to a considerable extent in the eggshell and in the bones. Shipley (loc. cit.) and coworkers pointed out that this mineral cannot replace calcium in normal *bone formation*. Kenney and McCollum (loc. cit.) confirmed these observations. Drea (loc. cit.) showed that strontium is one of the elements which pass from the food and water into the hen's blood and egg, and then into all of the tissues of the embryo.

The cyclotron (Lawrence *et al.*[3]) has made available a supply of the radioactive isotopes of calcium ($_{20}Ca^{45}$) and strontium (Sr^{89}). By means of these Pecher[1,6a,7] was able to resolve the results of classical investigations into a quantitatively accurate formulation of the exchange of calcium and strontium. He found that:

1. Of a dose of radioactive calcium, 58% was recovered from the skeletons of mice after 24 hours. Of a dose of radioactive strontium, 33% was similarly recovered.[6]

2. In the case of both radioactive strontium and radioactive calcium the activity of the skeletons of mice indicated that nearly maximum uptake was reached 8 hours after intravenous administration.[6]

3. Bone uptake of radioactive calcium and radioactive strontium was nearly three times as great following intravenous administration as that following oral administration.[6]

4. Radioactive calcium and strontium originally fixed in the skeletons of mice was found to migrate to the fetuses during the last days of pregnancy and to be transferred to offspring through lactation.[7]

5. Radio-strontium administered intravenously to lactating cows was recovered in the milk in the amount of about 10% of the dose, during the first 4½ days following administration.[1]

The demonstration of the selective localization of calcium and strontium in bone has suggested strongly the application of the radioactive isotopes of these minerals to clinical metabolic studies and possibly to therapeutic bone irradiation. Because of its relatively greater availability radioactive strontium has been selected for this purpose. Pecher[6b] has reported clinical and postmortem studies with radioactive strontium on a group of cases of carcinoma with demonstrated bone metastases.

Figure 1 demonstrates the method of treatment usually employed in these cases. Response of the red blood cell level is shown. The

lowering of the phosphatase* value and its maintenance at a point only slightly above the normal limit over a considerable period of time is also indicated.

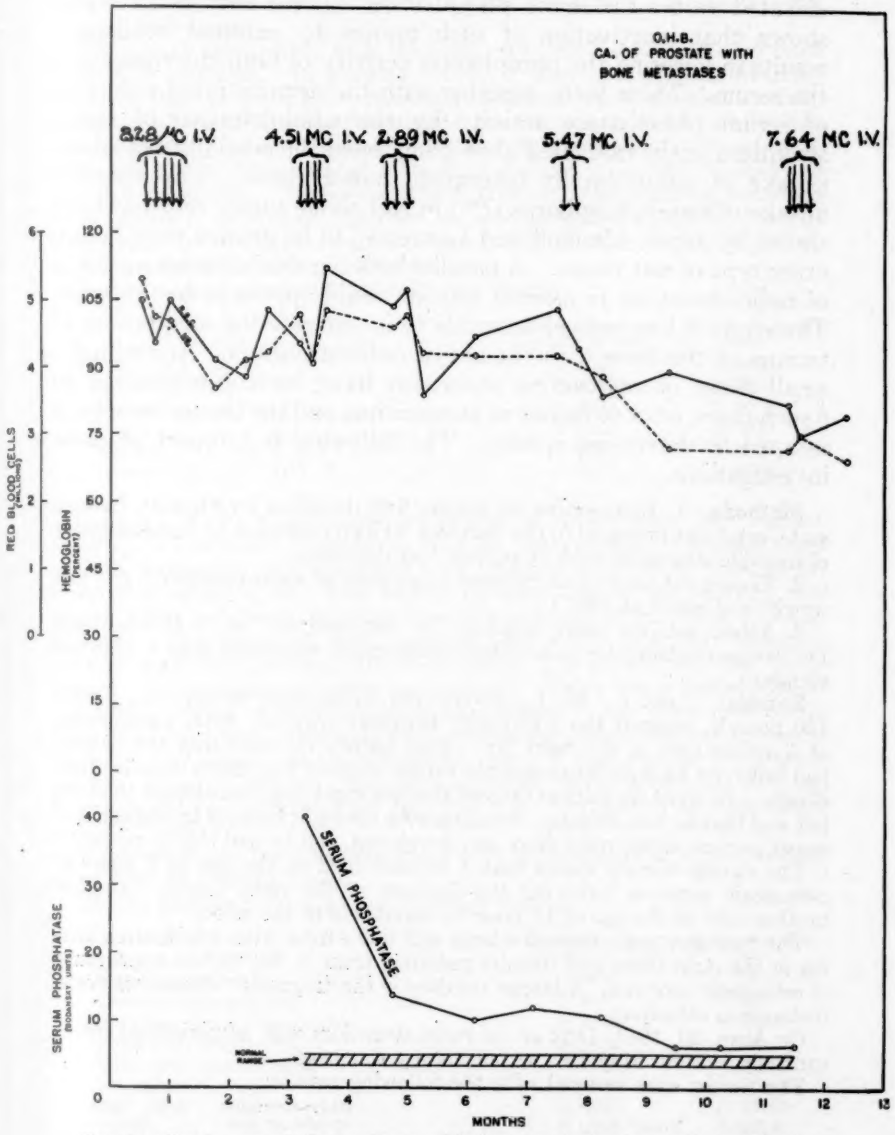

FIG. 1.—Carcinoma of the prostate with bone metastases: response of serum phosphatase, hemoglobin and red blood cell levels to radio-strontium therapy. (Arrows indicate fractioning of total doses shown.)

* Phosphatase activity was estimated by the method of Bodansky (J. Biol. Chem., 99, 197, 1932; **101**, 93, 1933) for the determination of alkaline serum phosphatase activity.

The recent work of Woodard and Higinbotham[10] has demonstrated high phosphatase values in osteogenic tumors. In many such cases the phosphatase activity of the tissue is reflected in elevated values for serum phosphatase. These authors have also shown that inactivation of such tumors by external irradiation results in lowering the phosphatase activity of both the tumor and the serum. These facts, together with the demonstrated reduction of serum phosphatase activity by the administration of radio-strontium in the case cited above, suggested the possibility of a high uptake of strontium by osteogenic tumor tissue. The selective uptake of radio-phosphorus (P^{32}) in soft tissue tumor cells has been shown by Jones, Chaikoff and Lawrence[2] to be greater than in any other type of soft tissue. A parallel between this behavior and that of radio-strontium in osseous tumors would appear to be probable. Therefore, it has seemed desirable to investigate the metabolism of tumors of the bone with the aid of radio-strontium. Accordingly, small doses of radioactive strontium have been administered to 6 such cases, prior to biopsy or amputation, and the tissues have been assayed to determine uptake. The following is a report of these investigations.

Methods. 1. Radioactive strontium, first described by Stewart, Lawson and Cork,[8] was prepared in the Berkeley 60 inch cyclotron by bombardment of metallic strontium with 16 million volt deuterons.

2. Tissues for assay were reduced to aliquots of approximately 1 gm. wet weight and ashed at 400° C.

3. Ashed samples were assayed for radioactivity on a standardized Du Bridge electrometer or a Geiger counter and compared with a uranium standard.

Results. Case 1. W. L., 17-year-old white male school boy, weight 130 pounds, entered the University Hospital May 15, 1941, complaining of constant pain in the right hip. Past history revealed that the patient had fallen on his right hip 6 months earlier without immediate serious after-effects. In April the patient noticed that the right thigh was longer than the left and that he was limping. Swelling over the right femoral trochanter and upper portion of the right ilium had developed, and he had lost 15 pounds.

The family history shows that 1 brother died at the age of 7 years of osteogenic sarcoma following the fracture of the right femur. Another brother died at the age of 12 years of carcinoma of the colon.

The roentgenogram showed a large soft tissue mass with calcification arising in the right ilium and spicules radiating from it, the typical appearance of osteogenic sarcoma. A biopsy resulted in the diagnosis: chondrosarcoma (osteogenic sarcoma).

On May 20, 1941, 1462 μc. of radio-strontium was administered intravenously, and on May 29 a second biopsy was taken.

The tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Muscle (normal?)	0.1475	0.010
Fat	0.00663	0.00045
Bone (apparently uninvolved)	0.244	0.0166
Bone and marrow	0.1948	0.0131
Bone (infiltrated)	0.498	0.034
Tumor	0.361	0.0246
Blood clot	0.0684	0.0046
Skin (normal)	0.342	0.0223

CASE 2. C. L., a 27-year-old white male, weight unknown, was admitted to the University Hospital in April, 1941. Past history showed that he had a spiral fracture of the right femur in 1937. One month later a roentgenogram of the knee joint revealed a tumor involving the external condyle. This was diagnosed radiologically as a giant cell tumor. No biopsy was made at that time.

The patient was treated with Roentgen ray, and the area became more dense and quiescent. In February, 1941, a tumor was noted involving the lower third of the thigh. Roentgen ray examination revealed a chiefly extracortical tumor showing elevation of the periosteum and small "specks of calcification within the tumor." On Roentgen ray films taken in April, 1941, the tumor still appeared to be extracortical. The old fracture line was still discernible. Radio-strontium (1183 μc.) was administered *orally* April 29, 1941, at 11 P.M. Amputation was performed April 30, 1941, at 12.30 P.M. Microscopic examination resulted in the diagnosis: osteoblastic osteogenic sarcoma of the femur.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Skin	0.0064	0.00054
Fat	0.00361	0.0003
Muscle	0.0036	0.0003
Femur	0.0131	0.0011
Marrow	0.0094	0.00079
Tumor	0.0073	0.00061

CASE 3. W. R., a 13-year-old white male student (weight 107 pounds), entered the University Hospital on June 24, 1941, because of gradual onset of pain and tenderness associated with pressure of a tumor mass in the upper right tibia region. Past history revealed that he was perfectly well until 7 weeks previously, at which time he was struck in this region by a soft baseball. The immediate pain subsided after a few days only to return about 1 week later and gradually to progress. The patient was then hospitalized. Temperature on entry was normal. There was a rather diffuse, egg-sized swelling over the antero-medial aspect of the upper end of the right tibia with some increased local temperature, moderate tenderness to pressure, and dilation of the superficial veins. There was no lymphadenopathy. Biopsy (June 26): osteogenic sarcoma. Radio-strontium (357 μc.) was administered intravenously July 2, 1941. Amputation was performed on July 7, 1941.

Figure 2 shows the roentgenogram and autoradiograph of the section submitted for activity assay.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Femur spongiosa	0.0066	0.0018
Femur epiphyseal line	0.106	0.029
Cartilage (femur epiphysis)	0.0318	0.0088
Bone with tumor (front)	0.1461	0.041
Bone with tumor (back)	0.1586	0.044
Muscle	0.0052	0.00146
Fat	0.0002	0.00005
Tumor	0.0996	0.0279
Skin	0.0772	0.0215
Femur cortex	0.0542	0.015

CASE 4. R. W., a 9-year-old white female (weight 85 pounds), was admitted to the University Hospital February 21, 1941. About 3 months prior to admission a small hard swelling was observed over the distal portion

of the ventral surface of the right forearm. This was not painful and did not appear to be inflamed. The motion of the wrist was not restricted. There was no history of trauma or injury. A Roentgen examination was made, and a diagnosis of bone tumor resulted. On a biopsy, the diagnosis of

a *b*

FIG. 2.—*a*, Roentgenogram of section of leg (Case 3). *b*, Autoradiograph of section of leg (Case 3), showing concentration of Sr_{89} in tumor and at epiphyseal line.

Ewing's tumor of the radius was established. A series of Roentgen ray treatments was instituted immediately over the extremity and the chest, and the local mass disappeared almost completely. Roentgen examination, however, still revealed evidence of a tumor in the right forearm. Pain had developed during the 3 weeks prior to this examination. At the time of

admission there appeared to be no abnormality in the contour of the right forearm, by observation or palpation. There was no tenderness. About 9 months after the first admission the patient returned because of a rapidly increasing mass involving the right forearm. There was no tenderness except on very firm pressure. Roentgen examination revealed a definite increase in the tumor mass involving the right radius so that the entire shaft was then involved. There was extensive invasion of the soft tissues. No metastasis to the lungs was demonstrated. Radio-strontium (326 μc.) was administered intravenously September 25, 1941. Amputation was performed September 30, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Cortex of ulna (normal bone)	0.032	0.0098
Epiphyseal lateral humeral condyle (normal)	0.02442	0.007
Tumor, sample 1 (of radius)	0.0106	0.0032
Tumor, sample 2 (of radius)	0.0122	0.0033
Fat	Trace	
Muscle	Trace	
Skin	Trace	

CASE 5. O. E., a 54-year-old white male (weight 131 pounds), was admitted to the University Hospital August 22, 1941. About 18 months prior to admission the patient had developed pain in the posterior gluteal region over the sciatic notch. At the same time he developed a limp of the left leg. Six months later the pain had extended down to the inner aspect of the left knee. The left leg became weak and there was considerable muscle atrophy of the lower left extremity. During the 6 months preceding admission there was constant pain involving the left hip and the upper portion of the left thigh. There was moderate obstipation and 40 pounds loss in weight. On admission, examination revealed a large firm mass palpable in the lower left quadrant. There was considerable muscle atrophy of the left lower extremity. The motion of the extremity at the hip was limited in all directions. There was diminished pain to touch over the distribution of the left second and third lumbar segments with motor loss and atrophy of the abductors and of the flexors of the thigh. The left knee jerk was absent. Roentgen examination of the pelvis showed an extensive lesion of the bone involving the left ilium, ischium, and inferior pubic ramus. There was expansion of bone; moderate areas of bone destruction; periosteal thickening; and new bone formation. The appearance was strongly suggestive of osteogenic sarcoma. Radio-strontium (582 μc.) was administered intravenously September 3, 1941. A biopsy was performed September 9, 1941.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Bone tumor	0.483	0.082
Subcutaneous tissue and fascia (involved)	0.098	0.0016
Muscle	0.0124	0.0021
Skin	0.0086	0.0014
Fat	?	

CASE 6. C. B., a 21-year-old white male (weight unknown), was admitted to the University Hospital August 4, 1941. Seven months prior to admission the patient was struck by a heavy piece of metal which produced an ecchymotic area over the outer aspect of the right thigh and which seemed of no consequence. About 2 months later a slight swelling was observed. At the same time a pain developed in the region of the right thigh, but this was not severe enough to incapacitate him. One month prior to admission

the pain became more intense. An operation was performed and an encapsulated tumor was removed. This was diagnosed as myxo-fibro-osteosarcoma. Physical examination on admission revealed a firm, somewhat tender mass measuring approximately 10 cm. in diameter, directly above the incision resulting from the previous operation. On palpation the mass could not be clearly demarcated from the surrounding tissues. There was no evidence of inguinal metastasis. Roentgen examination revealed no metastasis to the parenchyma of the lungs, but examination of the upper

TABLE 1.—UPTAKE OF RADIO-STRONTIUM—MICROCURIES PER GM. AND % OF DOSE PER GM.—TISSUE—WET WEIGHT

	Case 1. W. L.	Case 2.* C. L.	Case 3. W. R.	Case 4. R. W.	Case 5. O. E.	Case 6. C. B.
Normal bone: μc./gm.	0.244	0.0131	0.0542	*a.* 0.0320 *b.* 0.0244	..	0.078
% dose/gm.	0.016	0.0011	0.015	*a.* 0.0098 *b.* 0.0070	..	0.012
Infiltrated bone: μc./gm.	0.0498	0.0073	*a.* 0.1461 *b.* 0.1586			
% dose/gm.	0.034	0.0006	*a.* 0.041 *b.* 0.044			
Tumor: μc./gm.	0.0361	..	0.0996	*a.* 0.0106 *b.* 0.0122	0.0483	0.588
% dose/gm.	0.0246	..	0.0279	*a.* 0.0032 *b.* 0.0033	0.082	0.090
Skin: μc./gm.	0.342	0.0064	0.0772	trace	0.0086	
% dose/gm.	0.022	0.0005	0.0215	..	0.0014	
Muscle: μc./gm.	0.1475	0.0036	0.0052	trace	0.0124	0.0005
% dose/gm.	0.010	0.0003	0.0014	..	0.0021	0.0007
Fat: μc./gm.	0.0066	0.0036	0.0002	trace	?	
% dose/gm.	0.0004	0.0003	0.0005			

* The short interval between administration of radio-strontium and amputation (12 hours) together with the fact that the radio-strontium was given orally probably accounts for the small uptake in all tissues.

right thigh showed a soft tumor mass in the upper portion of the thigh just below the trochanteric line. There was also an irregular area of calcification measuring approximately 6 by 3 cm. which was lateral and slightly posterior to the shaft of the femur. It appeared to have no connection with the femoral shaft. Radio-strontium (650 μc.) was administered intravenously August 2, 1941. An operation was performed August 6, 1941, and a tumor measuring 5 by 4 by 3 cm. was removed together with the surrounding muscle. There was no histologic evidence of malignant tumor in these tissues.

Tissues were assayed with the following results:

Tissue	Radio-strontium uptake, μc./gm.	%/gm. tissue of dose
Bone (uninvolved)	0.078	0.012
Tumor	0.588	0.090
Muscle	0.005	0.0007

Discussion. Despite the marked difference in the uptake of radio-strontium by various tissues, there is ample evidence that the maximum occurs in bone and tumor tissues. In soft tissues variation is especially noticeable, but a somewhat striking concentration is observed in several of the cases in the skin. This has suggested the desirability of investigating the rôle of the skin in strontium metabolism. Such studies are now in progress in this laboratory. It is noteworthy that different parts of the tumor show marked differences in the uptake of strontium. This might be due (apart from causes such as vascularization, regressive local changes, and so on) to difference in the metabolic rate in different parts of the tumor,

depending on the state of cell development at the time of biopsy. The high uptake of strontium in areas where new bone is being laid down, whether this be normal or neoplastic, indicates that radioactive strontium will provide a valuable tool in the study of bone healing after experimental fractures. As with radioactive phosphorus in the case of new soft tissue cells, the rate of the laying down of new bone cells can be determined with labelled or radioactive strontium.

In order to evaluate the radiation effects of large doses of radio-strontium and to compare them with the effects of external sources of radiation such as Roentgen rays, it is desirable to attempt to convert the radiation emitted by radio-strontium into *r* units. This can be estimated from the energy of the emitted particles. Radio-strontium emits beta rays. Its half life is 55 days and its mean average life is 79.6 days. The maximum energy of radiation is 1.5 MEV. The particles from radioactive substances, however, have different energies (continuous spectrum); therefore, the mean energy values must be taken into calculations. For radio-strontium this is 0.75 MEV. According to this energy per particle: *One microcurie of radio-strontium yields 38 r units daily per gram of tissue,* assuming uniform distribution. However, strontium is taken up mainly by osseous tissue, so that the radiation is concentrated chiefly in bones and osteogenic cells.

It would appear from the foregoing that indications exist for the experimental therapeutic use of radio-strontium in cases of certain bone tumors. Particularly this would appear to be justified in view of the exceedingly bad prognosis in such cases, and because of the meagre resources which now exist for their treatment. Because of the known high resistance of bone neoplasms to radiation, experience may prove that radio-strontium has therapeutic value chiefly as an adjunct to external radiation (Roentgen rays, radium, neutrons), as a means of increasing total radiation to the affected areas.

Pursuant to these ideas, radio-strontium is now being applied therapeutically in several of the cases here reported and in several patients suffering from skeletal prostatic metastases. Later publications will describe these clinical studies.

Summary and Conclusions. 1. Investigations concerning the metabolism of calcium and strontium by means of their inert and radioactive forms have been reviewed.

2. Preliminary clinical studies with radioactive strontium in breast and prostatic carcinoma with bone metastases are reported.

3. Administration of radioactive strontium to 6 cases of bone tumor prior to biopsy or amputation shows uptake chiefly by growing bone and by osteogenic tumor tissue.

4. Various considerations seem to justify the therapeutic use of radioactive strontium in certain bone tumors. Clinical studies along this line are now in progress and will be reported at a later date.

We wish to express our appreciation to the staff of the Radiation Laboratory, and particularly to Dr. Martin Kamen, for generous coöperation in supplying radioactive strontium used in this study. We are indebted to Dr. Joseph Hamilton for the autoradiograph shown in Figure 1, and we wish to thank Drs. Leroy Abbott, Keene Haldeman and other members of the Department of Orthopedic Surgery of the University of California Hospital for permitting us to carry on these studies on their patients.

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THE TOLERANCE OF RABBITS FOR THE AGGLUTINOGEN AND THE TOXINS OF HEMOPHILUS PERTUSSIS*

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Control of communicable disease requires either effective suppression of dissemination of the causal agent or adequate means of increasing the resistance of the population at risk. In the case of the air-borne diseases, measures directed toward controlling dissemination, such as ultraviolet irradiation and germicidal vapors, while promising, are still not operative on a scale significant to public health.

The practicability of increasing resistance to any disease is greatly influenced by the availability of (1) means of determining the distribution of susceptibility, and (2) an innocuous immunizing agent.

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In the case of whooping cough there has been no suitable test for individual susceptibility, and the whole bacterial vaccine used to immunize is not entirely free from undesirable side reactions.

Work conducted at the University of Pennsylvania for a number of years has been directed toward preparation of suitable diagnostic and immunizing reagents from *Hemophilus pertussis*. An agglutinogen has been prepared in a considerable degree of purity from *H. pertussis* of Phase I; this agglutinogen is highly antigenic; when injected into the skin of non-immune animals or human beings, it has not caused reactions.[6b] In the hands of Flosdorf, Felton, Bondi, and McGuinness[5] this purified agglutinogen has shown promise as (1) a test reagent for estimation of individual susceptibility, and (2) as a stimulating injection for increasing active immunity. The present study has elicited no evidence of this agglutinogen being significantly toxic when administered intravenously to rabbits.

Physical disintegration of cells of *H. pertussis* by sonic vibration was used to insure that no possibly significant labile factors initially in the cells would be lost. By such delimiting means a stable agglutinogen was found to be liberated. Although the agglutinogen is stable, sonic extraction has been continued as the means of liberation of the agglutinogen because of its convenience. Other components of the bacterial cell are also brought into solution in the sonic extract. One of these soluble components is a thermolabile toxin which has been shown to give a strong reaction of primary toxicity on injection into the skin of rabbits.[4,6b] Storage of the pertussis cells or of their extracts or heating the extracts to 56° C. for 30 minutes destroys or alters the thermolabile toxin, leaving a less powerful thermostable toxin. Whether the thermolabile and thermostable toxins exist separately or in combination in the *H. pertussis* cell, or whether the thermostable toxin is an alteration product of the thermolabile component is not known. Both thermolabile and thermostable toxins are shown in the present study to cause pathologic changes on injection into rabbits.

Methods and Terminology. Washed cells of *H. pertussis* suspended in distilled water are disintegrated by the action of the sonic vibrator;[7] the resultant material is centrifugalized. The opalescent supernatant fluid is called the *sonic extract;* it contains agglutinogen, thermolabile toxin and thermostable toxin. Heating of the sonic extract for 30 minutes at 56° C. inactivates the thermolabile toxin, leaving thermostable toxin and agglutinogen. This preparation is called *heated sonic extract.* The agglutinogen has been purified from these toxins as previously described.[6b] In text and in tables, injection of *agglutinogen* implies this purified preparation.*

In the tables the amounts of materials injected are expressed both in milligrams of dry substance and in units of agglutinogen contained in them. The purified agglutinogen is assigned a unit value in terms of its capacity to combine agglutinin in quantitative absorption experiments;[6a] 1 unit of

* In describing in detail the preparation and properties of these several materials in earlier publications,[4,6b,8] the *sonic extract* was referred to as *SX–I*, the *heated sonic extract* as *heated SX–I*, the *purified agglutinogen* as *A–I*, the *thermolabile toxin* as *TLT* and the *thermostable toxin* as *TST*.

TABLE 1.—THE LETHAL DOSE OF VARIOUS PREPARATIONS OF *H. pertussis* WITH THE CHANGE IN WEIGHT AND THE FORMATION OF AGGLUTININS FOLLOWING INTRAVENOUS INJECTIONS

Preparations	Dose			Number of animals			Change in weight (%)				Agglutinin titer
							Last living		At autopsy		
	Units of agglutinogen*†	Total solids (mg.)‡	Number of doses	Used	Died	Survived	Range	Av.	Range	Av.	
Sonic extract	6	.25	2 to 5	3	3	0	−8 to −17	−14	±0 to −16	−8	
	3	.12	6 to 12	6	1	5	+1 to −18*	−4*	+8 to −21*	−4*	120 to 160*
	300	12.5	1	2	2	0					
	30	1.25	1	3	3	0					
	6	.25	1	5	0	5	...	..	±0 to −10	−4	0 to trace**
	3	.12	1	2	0	2	...	..	...	..	20 to 80
Sauer's vaccine	50	2.5	3 to 4	2	2	0	−5 to −14	−9.5	−11 to −17	−14	
	25	1.3	6 to 12	4	1	3	±0 to −4*	−2*	±0 to −11*	−4*	2,560 to 10,240*
	200	10.0	1	2	2	0	...	..	−8 to 13	−10.5	
	100	5.0	1	6	5	1	...	..	−11 to −22*	−16.5†	
	50	2.5	1	7	1	6	...	..	+3 to −13*	−3*	160 to 2,560††
	25	1.3	1	2	0	2	...	..	...	..	2,560 to 5,120
	10	.5	1	2	0	2	−3 to −9	−6	...	..	640 to 2,560
Heated sonic extract	300	20.0	3 to 7	4	3	1	−9 to −11‡‡	−10‡‡	−4 to −19‡‡	−11‡‡	
	150	10.0	6 to 12	5	1	4	−5 to −14*	−10*	−3 to −21*	−12*	80 to 2,560
	1,500	100.0	1	2	2	0	...	..	±0 to −5	−2.5	
	300	20.0	1	5	1	4	...	..	+4 to −5*	−2*	20§
	150	10.0	1	5	1	4	...	..	...	..	trace to 1,280*
Purified agglutinogen	2,000	6.0	3	2	0	2	+2 to −10	−4	+3 to −12	−4.5	80 to 160
	1,000	3.0	6	2	0	2	+4 to −6	−1	−2 to −8	−5	
	200	.6	12	2	0	2	−4 to −9	−6.5	+2 to ±0	+1	1,280 to 2,560
	4,000	12.0	1	1	1§§	0	...	..	...	−1	
	3,500	10.5	1	1	0	1	...	..	...	−1	20*
	2,000	6.0	1	2	1§§	1	...	..	−1 to −10	−5.5	80*

* Only animals that survived.
** 3 out of 5 animals.
† 2 out of 5 animals that died.
†† 4 out of 6 animals that survived.
‡ Determined in salt-free solution (or suspension of organisms).
‡‡ Only animals that died.
§ 2 out of 4 animals that survived.
§§ Death not due to injection, see text.
*† Estimated in case of Sauer's vaccine on basis of extractable agglutinogen; 1 ml. containing 10^{10} organisms is equivalent to 10 units of agglutinogen.

the purified agglutinogen solution usually contains 0.001 or 0.002 mg. of total solids. The purpose of listing the units of agglutinogen in the sonic extracts is to afford a comparison of the toxicity of the thermolabile and thermostable toxins contained in these extracts in relation to the content of agglutinogen.

Chinchilla rabbits weighing about 2 kg. were injected with single doses or with repeated daily doses of various quantities of purified agglutinogen or of sonic extract or heated sonic extract. Animals which were sacrificed were killed by ether. Pieces of heart, spleen, liver, brain, lungs, kidneys, adrenals, and popliteal lymph nodes were fixed in formalin. The sections were stained with hematoxylin-eosin, and sections of the liver were stained for fat, and sections of the spleen for iron.

TABLE 2.—LETHAL DOSES OF VARIOUS FRACTIONS OF H. PERTUSSIS EXPRESSED IN UNITS OF AGGLUTINOGEN

	Single injections	Repeated daily injections
Sonic extract	**6–30***	**3–6**
Sauer's vaccine	**50–100**	**25–50**
Heated sonic extract	**300–1500**	**150–300**
Purified agglutinogen	>3500	>2000

* The boldface data are closer to the exact lethal doses than those not boldface.

Results. Some results of the study are presented in Table 1. They include the lethal doses, the changes in the weight of the animals, and the agglutinin titers. In order to facilitate the interpretation of the data, summaries of certain findings and the results of some calculations are presented in subsequent tables.

Lethal Doses. From the data in Tables 1 and 2, it will be observed that the range of lethal doses varies from, in the case of the sonic extract, a quantity containing 6 to 30 units of agglutinogen up to a quantity of purified agglutinogen representing 3500 units of agglutinogen injected as a single dose. In the case of repeated daily doses, the lethal range varied from 3 to 6 units in the case of sonic extract to more than 2000 units of purified agglutinogen. It is true that Rabbit 270 died after 2000 units of purified agglutinogen, and Rabbit 275 after 4000 units. However, both these experiments were performed during the last days of July, 1941, when the animals suffered greatly from heat. Moreover, other rabbits receiving 3500 units, or repeated doses of 2000 units, not only survived, but also showed no change in blood picture and no tissue reaction.

Changes in Weight. All animals that succumbed to injection of the sonic extracts lost considerable weight (Table 1). If they died 1 to 2 days after the first injection, they were found to have lost an average of 9%, while after 6 to 7 injections this loss amounted to 25%. The animals which survived, on the other hand, showed little if any change in weight. As a matter of fact, only 1 of these animals was found to lose more than 6% during the first day following a single injection, and only 1 lost more than 9% during the first 6 days of repeated daily injections, the average weight loss amounting to as little as 3% in the former group, and 4% in the latter.

TABLE 3.—ERYTHROCYTE AND LEUKOCYTE CHANGES AFTER SUBLETHAL DOSES OF VARIOUS PREPARATIONS OF H. PERTUSSIS

Preparations	Dose			No. of rabbits	Number of erythrocytes (millions)					Hemoglobin (%)					Number of leukocytes (thousands)					Number of granulocytes (thousands)					Number of lymphocytes (thousands)				
					Control		Days after injection *			Control		Days after injection *			Control		Days after injection *			Control		Days after injection *			Control		Days after injection *		
	Agglutinogen, units	Total solids (mg.)	Repeated, times		1st	2d	2–3	5–6		1st	2d	2–3	5–6		1st	2d	2–3	5–6		1st	2d	2–3	5–6		1st	2d	2–3	5–6	
Sonic extract	6	0.25		352	6.1	6.0	5.9	6.3		77	78	74	80		3.9	3.9	18.0	14.4		.5	1.1	3.4	2.2		3.2	2.6	14.2	12.0	
				351	5.9	6.3	6.1	5.8		84	79	79	82		4.6	4.9	7.6	7.7		2.0	2.3	2.6	1.6		2.0	2.1	4.6	5.9	
	3	0.12	6	358	6.0	6.0	5.8	5.0	6.1	68	81	79	70	81	3.9	3.15	6.45	5.25	6.4	1.4	1.4	1.1	1.4	1.7	2.2	1.6	5.2	3.5	4.5
			6	357	6.2	5.9	5.3	5.3	6.25	81	78	78	71	78	5.35	3.95	5.45	7.0	5.7	.8	1.2	1.1	3.2	1.7	4.3	2.4	3.8	3.5	3.4
	3	0.12		366	5.7	6.9	5.45	5.9		78	80	76	74		4.85	6.35	7.45	7.15		.9	2.35	2.6	1.9		4.2	3.7	4.3	4.8	
				367	4.85	5.3	5.65	5.2		79	70	76	77		4.7	4.95	4.2	6.05		1.3	1.7	1.8	1.1		3.2	3.2	2.1	4.7	
Sauer's vaccine	50	2.5		356	6.3	6.8	5.5	5.3		90	83	75	82		4.1	3.5	20.4	12.45		2.4	1.5	5.7	3.6		1.6	1.8	13.1	8.6	
				355	5.3	4.5	4.9	4.2		72	70	65	64		4.35	3.9	19.25	14.4		1.5	1.1	2.7	3.7		2.6	2.5	15.8	10.4	
	25	1.3	6	362	5.2	5.25	4.5			68	70	75			2.4	5.0	10.7			.8	3.8	6.2			1.4	.85	3.9		
			6	361	5.8	4.55	4.15	2.65	2.9	73	65	62	40	48	4.9	4.75	13.55	12.35	7.2	2.1	1.7	5.7	5.8	2.7	2.4	2.7	6.8	5.9	4.0
	25	1.3		370	4.8	5.1	5.4	5.5		81	74	76	76		4.2	3.6	9.4	7.95		1.1	1.0	1.6	3.0		2.6	2.4	7.3	4.6	
				369	5.7	5.35	6.6	5.5		79	75	80	81		5.0	6.5	10.4	7.9		1.35	1.8	2.2	2.0		3.6	4.4	7.9	5.5	
	10	0.5		375	6.6	6.3	5.7	5.9		74	71	88	78		4.0	4.15	11.05	9.7		1.6	1.9	5.9	2.4		2.0	2.0	4.3	6.3	
				376	4.05	4.3	5.65	3.8		61	73	76	78		2.3	3.45	6.05	3.75		1.0	1.3	2.9	1.4		1.15	1.9	2.7	2.2	
Heated sonic extract	300	20.0		354	5.75	5.6	4.9	5.0		77	72	70	70		3.6	3.4	7.75	7.3		1.45	1.6	1.7	2.7		2.0	1.7	5.3	3.8	
	150	10.0	6	360	5.2	4.35	4.55			62	66	66			2.8	4.65	12.0			.8	1.5	5.9			1.7	3.0	5.3		
			6	359	5.6	5.5	5.35	5.2	5.2	72	73	73	64	66	3.25	3.55	11.2	7.1	4.75	.8	1.0	3.2	1.9	1.4	2.1	2.2	6.9	4.3	2.8
	150	10.0		368	5.1	5.6	5.5	4.5		67	64	63	65		3.7	3.55	8.45	6.05		1.0	1.2	6.4	2.7		2.3	2.2	1.6	2.6	
				373	6.3	6.6	6.5	6.0		79	80	96	77		3.75	4.9	7.35	4.95		1.35	1.9	4.9	2.7		2.1	2.8	2.1	1.7	
				372	5.7	5.1	6.1	5.9		82	74	84	81		7.25	7.35	10.05	8.4		2.4	1.8	4.0	2.6		4.3	5.1	5.7	5.3	
				374	3.55	3.4	3.2	3.6		58	52	54	67		4.9	4.85	6.6	5.9		3.3	2.9	4.3	2.8		1.1	1.6	2.0	2.4	
Purified agglutinogen	3500	10.5		371	5.65	5.2	5.6	5.3	6.0	84	79	84	75	85	4.5	4.15	4.1	5.2	4.8	.7	.9	1.0	1.6	1.4	3.5	2.9	2.8	3.2	3.2
	2000	6.0	3	274	5.6	5.1	4.4	5.6		80	80	70	71		5.1	5.6	6.2	5.7		1.3	1.1	1.3	2.7		3.3	4.2	4.6	2.8	
	2000	6.0		364	5.3	5.55	5.3	5.1	5.1	72	78	79	67	71	3.4	3.55	4.4	5.95	3.95	1.3	1.3	2.1	1.8	1.3	1.9	2.0	1.7	3.9	2.4
	1000	3.0	6	289	5.9	6.3	5.7	5.85	5.6	83	83	73	75	73	2.9	4.15	4.2	6.4	6.3	.7	.9	.8	2.9	2.4	2.2	2.9	3.0	2.8	3.6
			6	288†	5.95	6.15	5.7	5.5	5.4	85	92	76	74	82	6.8	8.9	14.55	14.7	8.1	1.5	5.0	5.1	9,0	4.0	4.8	2.7	8.3	4.7	3.6

* In animals that received repeated injections these columns refer to 3, 7 and 10 days after the first injection.
† Rabbit 288 suffered from an acute echinococcus infection of the omentum.

Changes in the Blood. The behavior of the red and white blood cells was studied in 26 rabbits which received sublethal doses of the several preparations (Table 3). A slight drop in the number of erythrocytes and hemoglobin percentage was observed in all animals which received the highest sublethal doses; those which received lower doses did not show this change. A leukocytosis was found after single doses of sonic extract containing 6 units of agglutinogen, of Sauer's vaccine containing 10 to 50 units, and of heated sonic extract containing 150 to 300 units, as well as after repeated doses of Sauer's vaccine containing 25 units and sonic filtrate containing 30 units. The lymphocytes rose highest after Sauer's vaccine, and remained low in most cases injected with heated sonic extract. The granulocytes rose highest after injection of heated sonic extract and remained low after injection of sonic extract. In other words, after injection of sonic extract the leukocytosis was almost exclusively a lymphocytosis, and with Sauer's vaccine a lymphocytosis and granulocytosis, while after injection of heated sonic extract it was, in most cases, predominantly a granulocytosis. After injection of purified agglutinogen no leukocytosis was observed.

Organ and Tissue Changes. If we turn now to the individual organs and tissues and first consider the *weights of the organs* where these were taken (Table 4), it may be observed that lungs, spleen and kidneys showed a considerable rise in weight, and liver and heart a moderate increase, in all animals that succumbed to injections; while the animals which survived showed no distinct change in weight except in the spleen, the weights of which were double or almost double the normal weights in the rabbits which received Sauer's vaccine or heated sonic filtrate. These differences were apparent not only in the absolute weights of the organs, but also in the relative weights, *i. e.*, grams per kilo of body weight, whether these were calculated from the initial weights of the rabbits before they were injected (relative weights I), or from the final weights determined at the time of death (relative weights II) (Table 4).

TABLE 4.—CHANGES IN WEIGHT OF ORGANS EXPRESSED IN PER CENT OF NORMAL*

	Lung	Spleen	Kidneys	Liver	Heart
After Lethal Doses.					
Absolute weights	+80	+50	+54	+11	+11
Relative weights I	+86	+60	+59	+14	+13
Relative weights II	+105	+80	+78	+29	+26
After Sublethal Doses.					
Absolute weights	+12	+40	+11	+2	+2
Relative weights I	+5	+40	+6	+4	−4
Relative weights II	+10	+40	+11	+7	±0

* Changes in absolute weights were calculated by comparing organ weights of sacrificed rabbits with those of normal rabbits. Relative weights refer to weights of organs per kilo of body weight; I refers to those compared with body weights at beginning of the experiment; II refers to those at the end, *i. e.*, after weight loss had occurred.

* In animals that received repeated injections these columns refer to 3, 7 and 10 days after the first injection.
† Rabbit 298 suffered from an acute echinococcus infection of the omentum.

While the increase in weight of the kidneys, the liver and the heart was chiefly due to cloudy swelling, the increase in weight of the spleens after lethal doses was mainly caused by hyperemia, and that of the lungs by both hyperemia and edema. Differences in weight as produced by the various fractions of *H. pertussis* were not discovered; however, the average weight increase was greater in animals which died after repeated injections than in those which succumbed to the first dose.

The most conspicuous *tissue changes which were observed after lethal doses* were necrosis in liver, adrenals and kidneys, as well as in the lymphatic tissue of spleen and popliteal lymph nodes (the only lymph node studied). In the liver, necrosis was present in all animals which succumbed to injections except in Rabbit 249 which died (as late as) 7 days after a single injection of Sauer's vaccine, and in the 2 rabbits which died during a heat spell following a large single injection of purified agglutinogen (Rabbits 270 and 275). In the adrenals necrosis was observed only in 4 out of 13 animals which died and whose adrenals were studied microscopically, and in the kidneys only in 3 animals. In the liver of 2 rabbits (242 and 243) and in the kidneys of 1 rabbit (360) the necrotic tissue was found to be calcified. This seems to indicate that at least in these rabbits the necrosis was produced by the first or one of the first of the repeated daily injections of the fractions used.

In the spleens, too, necrosis was present in almost all animals. In some we found merely increased nuclear decay in the Malpighian bodies; in others focal necrosis was observed in both the follicles and the lymph sheaths; while in most we found extensive necrosis throughout the white pulp. The red pulp was mostly observed to be hyperemic, and often contained large plasma drops and swollen macrophages. In animals which succumbed after repeated injections the structure of the spleen appeared to be markedly loosened, and the white pulp was much reduced in quantity.

In the popliteal lymph nodes the necrosis was not as conspicuous as in liver and spleen. Of 15 rabbits which succumbed to injections and the lymph nodes of which were studied microscopically, only 2 showed extensive necrosis with diffuse hemorrhages throughout the parenchyma, while 11 showed all transitions from increased numbers of pycnotic nuclei in the secondary nodules to marked necrosis of the cortex. In most animals, the nodes were markedly hyperemic, and the central sinuses were sometimes distended with lymph.

Among the animals which survived, on the other hand, necrosis in liver and adrenals was found only in Rabbit 232 which was killed 1 day after the highest single sublethal dose of heated sonic filtrate. It may very well be that this rabbit would have died spontaneously if it had not been sacrificed so shortly after the injection.

The most conspicuous *tissue changes of the animals which survived*

were hyperplasia of the lymphatic tissue particularly in the spleen, and foci of extramedullary myelopoiesis in spleen and liver. Lymphatic hyperplasia in the spleen with large so-called germinal centers was observed especially after single injections of Sauer's vaccine containing 50 to 100 units of agglutinogen or repeated injections containing 25 units; it was present in some and absent in other animals which received heated sonic filtrate or purified agglutinogen. After single or repeated injections of sonic filtrate containing 3 to 6 units of agglutinogen, the secondary nodules as well as the lymph sheaths remained undisturbed. A mild lymphocytic hyperplasia was observed also in the popliteal lymph nodes of the animals which were injected with Sauer's vaccine, but it was absent after heated sonic filtrate.

Foci of extramedullary myelopoiesis were most marked and regularly present in both spleen and liver, in all animals which survived repeated injections of sonic filtrate, Sauer's vaccine, and heated sonic filtrate. After single injections of these fractions, such foci were observed in 8 spleens and 5 livers among 16 animals, while after injections of purified agglutinogen they were found only in the spleens of 3 out of 8 animals. The latter, to be sure, may have been due to causes other than the injections.

As to *other tissue changes* which were observed in our rabbits, those in lungs and brain deserve mentioning. Foci of chronic interstitial or bronchial pneumonia were detected in 27 out of 60 experimental animals, and foci of encephalitis were found in 6 out of 39 experimental animals. Since both these lesions were equally common in all our experimental groups as well as in our control animals, their occurrence is regarded as coincidental.

Mesenchymal reactions in the vascular connective tissue of lungs, liver and spleen as observed after intravenous injections of large doses of killed staphylococci, streptococci or colon bacilli[2,3] were seen only in 6 experimental and 1 control animal and seemed to be entirely independent of the treatment which they received.

Finally, it should be mentioned that the fat and iron metabolism as apparent in liver and spleen from fat and iron stains were not significantly altered in the experimental animals. The amount of fat which was found in the liver varied greatly in the different experimental groups and individual animals; and the amount of iron that could be demonstrated in the spleen likewise varied considerably; though it was found to be higher in animals which survived than in those which died, and seemed to be higher in those which survived repeated injections. However, in no experimental group was the amount of iron to be found greater than in our control animals.

Discussion. The various fractions of *H. pertussis* which have been studied differed not only in their toxicity, but also in their rôle in the production of certain pathologic changes. Expressed by weight of total solids, unheated sonic extract was 80 times as toxic as heated sonic extract.

While the lethal effect of sonic extract was obviously principally due to the thermolabile toxin, that of the heated sonic extract, like that of Sauer's vaccine, was probably due to the thermostable toxin; the effect of purified agglutinogen cannot yet be analyzed because no dose large enough to be lethal could be given to establish it. As to the mechanism of the death after lethal doses, it appears that this was the same with all the preparations, because the animals which succumbed to injections all showed the same histologic changes,* namely congestion and edema of the lungs; cloudy swelling of kidneys, liver and heart; and necrosis especially of liver and the lymphatic tissue of the spleen. Though it may be that shock was a factor concerned, the necrosis of the lymphatic tissue, together with the well-known lymphocytotic effect of *H. pertussis* in man suggest a more specific mechanism.

The pathologic changes which are observed in blood and tissues in pertussis or in bronchitis as observed in human patients have not been seen in our animals. Lymphocytosis and granulocytosis, on the other hand, were regularly present after certain doses; and a mild anemia was observed after high sublethal doses; and there was hyperplasia of the lymphatic tissue especially of the spleen, and extramedullary myelopoiesis in liver and spleen.

As to the nature of the factors that caused these reactions, the data of Table 3 first seemed to confirm the conclusion of Camerer[1] that the lymphocytosis was caused by the thermolabile toxin. However, like Fukushima[9] and Tuta,[11] we saw lymphocytosis also in some animals which received heated extract, and a certain parallelism seemed to exist between lymphocytosis, agglutinogen units and agglutinin titers. The latter observation is of interest in the light of Takahaski's claim according to which the lymphocytosis produced by *H. pertussis* can be neutralized by the injection of pertussis immune serum.[10]

As to the reaction of the granulocytes in our experiments, it was noted that a granulocytosis was present after injection of heated sonic extract containing 150 units of agglutinogen but absent after 3500 units of purified agglutinogen, though in both these cases the total solids amounted to about 10 mg. each. This observation could be interpreted to indicate that the granulocytosis was not merely a function of the protein contained in the preparations, but was caused probably by the thermostable toxin.

If, finally, we attempt to determine the greatest non-toxic doses of the various fractions, much depends on whether we look upon granulocytosis and lymphocytosis observed in these animals as harmful or beneficial. If we regard them as beneficial, the greatest non-toxic doses of the fractions would lie close to the lower of the 2 lethal doses as given in Table 2; while if we regard them as harmful

* A few rabbits were injected with lethal doses of living organisms and the histologic changes which were observed in these were the same as those produced by sonic extract.

the greatest single non-toxic dose of sonic extract would contain 3 units of agglutinogen, that of heated sonic extract somewhat less than 150 units, and that of the purified agglutinogen more than 3500 units. In the latter case, according to this calculation, the purified agglutinogen would be less than one one-thousandth as toxic as the sonic extract of the whole virulent organisms.

Summary. The relative toxicity of certain fractions of *H. pertussis* as well as their rôles in the production of certain pathologic changes in blood and tissues have been studied experimentally in rabbits. The agglutinogen is important in establishment of antibacterial immunity and the purified agglutinogen is giving promise as a reagent for use in intradermal testing for susceptibility to whooping cough. The purified agglutinogen contains neither thermolabile nor thermostable toxin. No evidence of toxicity of the purified agglutinogen was found when tested in dosage 300 to 1000 times greater than the lethal dosage of the thermolabile toxin. Thus, there is a wide margin of safety in the clinical application of the purified agglutinogen.

In the blood, a mild transient anemia was observed after high sublethal doses, and a leukocytosis also after lower doses, of preparations containing one or both toxins. With sonic extract the leukocytosis was almost exclusively a lymphocytosis; with Sauer's vaccine both a lymphocytosis and granulocytosis; and with heated sonic extract in most cases predominantly a granulocytosis. The two leukocytoses, therefore, appear to be caused by different toxins of *H. pertussis*. It may well be that the thermostable toxin does not exist natively as such, but is in complex combination with the thermolabile toxin; the thermostable toxin may appear only as a result of the reaction by which the thermolabile toxin becomes inactivated. No leukocytosis was found after massive doses of purified agglutinogen.

The tissue changes after lethal doses of the toxins included congestion and edema of the lungs, cloudy swelling of kidneys, liver and heart, and necrosis especially in liver and lymphatic tissue of the spleen. In surviving animals there were lymphatic hyperplasia especially in the spleen, and extramedullary myelopoiesis in liver and spleen.

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THE EFFECT OF ACID AND ALKALINE SALTS ON SOME PATIENTS WITH RHEUMATOID ARTHRITIS

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Low grade edema, which is frequently part of the clinical picture presented by arthritic patients, is often ignored, and its rôle in the disease is not clearly understood. Scull and Pemberton[6] have called attention to this edema or "tissue swelling" and have observed that, with bed rest and a low carbohydrate diet, arthritic patients often experience relief of pain, decrease in joint swelling, and an increase in joint mobility concomitantly with the loss of water from the body.

It has also been demonstrated[4,5] that synovial fluid may be regarded as a dialysate of plasma containing mucin, and that the presence of edema from any cause may be associated with an increase in the volume of synovial fluid.[2] These observations suggest that the volume of synovial fluid of arthritic patients may be related to the volume of the extracellular fluid compartment of the body.

In this study the clinical effects of water loss occurring after diuresis by ammonium chloride, and the clinical effects of water retention resulting from the administration of sodium bicarbonate were observed in 5 patients with rheumatoid arthritis.

Procedure. Five female patients with chronic rheumatoid arthritis were studied. They were placed on a diet containing 150 gm. carbohydrate and 75 gm. protein. The caloric value of the diet was adjusted for each patient by adding sufficient fat so that 40% more than the basal caloric requirement as estimated from the tables of Dubois and modified by Boothby and Sandiford[1] was given. The diet was the same every day for each patient and prepared so that it contained less than 2.5 gm. sodium chloride. Water was unrestricted, although the daily water intake was estimated and the urinary output was measured. The patients were weighed daily on a balance accurate to 1 gm. Under these circumstances it can be assumed that changes in body weight reflect water loss or water retention.[3] All patients had been hospitalized for several weeks or months prior to the experiments, and the symptoms resulting from the arthritis remained unimproved. None had menopausal symptoms. The patients received no physiotherapy, and analgesics were administered upon request of the patient during the course of these experiments.

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The patients were examined every morning. The mobility of the affected joints was measured and expressed in terms of degrees of range of motion (the degree of maximum extension minus the degree of maximum flexion) the circumference of the joints was measured. The symptom of pain was evaluated by careful questioning of the patient and noting the frequency with which she requested analgesics.

After control joint measurements were made over a period of 3 to 5 days the patients were given 6 to 8 gm. ammonium chloride daily for varying lengths of time. The ammonium chloride period was followed by the administration of 6 to 8 gm. of sodium bicarbonate for 7 to 10 days, and the same observations were made. The experiment was concluded by repeating the administration of ammonium chloride.

Results. Table 1 shows the detailed data on Patient 1. The remaining 4 patients responded similarly and their summarized data are shown in Table 2. Although there were individual variations in clinical response to the administration of ammonium chloride and sodium bicarbonate, the character of the response was remarkably similar in each case.

TABLE 1.—DATA ON PATIENT B. R.*

Date, 1940	Period	Weight in (kg.)	Range of motion (degrees)			Circumference (cm.)		Pain
			Right knee	Left knee	Left elbow	Right knee	Left knee	
10-16	Control	48.3	30	40	64	36.4	32.5	++
10-19	"	48.0	30	40	63	36.5	32.5	++
10-20	NH_4CL	47.9	30	40	65	36.5	32.5	++
10-22	"	46.3	40	45	70	35.4	31.0	+
10-24	"	45.4	55	55	70	34.0	31.2	0
10-26	"	44.3	70	60	85	33.0	31.5	0
10-30	"	41.8	85	85	112	32.0	31.5	0
11- 3	$NaHCO_3$	41.9	84	90	110	31.4	31.2	0
11- 5	"	42.8	70	70	105	33.0	33.0	++
11- 8	"	45.2	64	65	50	35.0	35.0	+++
11-11	NH_4Cl	46.0	50	50	35	35.0	35.5	+++
11-13	"	44.5	60	70	50	34.5	35.0	++
11-16	"	42.0	80	65	65	33.5	33.5	0
11-22	"	40.8	86	85	70	34.0	32.5	0
11-30	"	42.0	80	82	70	34.0	33.0	0
12- 8	"	41.0	80	80	70	34.0	33.0	0
12- 9	$NaHCO_3$	41.7	80	80	75	34.0	33.0	0
12-11	"	43.0	50	70	70	34.0	34.5	+++
12-15	"	45.4	45	40	50	35.5	35.5	+++
12-16	NH_4Cl	46.2	40	42	50	35.5	35.5	+++
12-18	"	45.4	55	70	60	35.0	34.0	+
12-22	"	41.7	100	95	75	33.0	33.0	0

* Every other set of determinations has been omitted by editorial request, in order to save space.

In each case the period of ammonium chloride administration was characterized by a significant decrease in body weight which under the conditions of the experiment can be assumed to be mainly due to water loss from the body.[3] Associated with the water

loss there was a decrease in joint swelling as measured by the joint circumferences. In Cases 1, 2, and 3 there was also a progressive increase in the mobility of the joints. Cases 4 and 5 showed no significant change in mobility but Case 4 had relatively little impairment of joint mobility initially, and Case 5 had very severe joint destruction with some ankylosis. All patients experienced relief of joint pains during the period of ammonium chloride administration. Relief of pain occurred even though the range of motion was not significantly altered (Patient 5).

TABLE 2.—DATA ON 4 PATIENTS

	Control period, 3–5 days	NH_4Cl period, 23–33 days	$NaHCO_3$ period, 7–10 days	NH_4Cl period, 6–8 days
Patient (A. B.):				
Weight (kg.)	80.0	74.2	78.6	75.5
Right shoulder:				
Abduction (deg.)	30	80	65	90
Extension (deg.)	30	100	60	120
Right knee—circumference (cm.)	41.5	39.0	41.0	39.0
Left knee—circumference (cm.)	40.0	40.0	41.0	39.0
Pain	+++	0	+++	0
Patient (V. B.):				
Weight (kg.)	31.2	27.7	30.9	28.6
Right shoulder—abduction (deg.)	60	90	45	90
Right knee—range of motion (deg.)	80	155	112	150
Right knee—circumference (cm.)	29.5	28.0	31.0	29.5
Left knee—range of motion (deg.)	0	65	65	90
Left knee—circumference (cm.)	29.0	25.0	29.0	25.5
Pain	+++	0	+++	0
Patient (I. S.):				
Weight (kg.)	53.2	51.0	54.0	51.7
Right knee—circumference (cm.)	35.0	33.0	35.0	33.0
Left knee—circumference (cm.)	35.5	32.0	34.0	31.0
Right ankle—circumference (cm.)	26.5	23.0	25.0	25.0
Left ankle—circumference (cm.)	26.5	24.0	27.0	25.0
Pain	0	0	+++	0
Patient (A. K.):				
Weight (kg.)	59.3	57.9	59.1	57.1
Right shoulder—extension (deg.)	135	170	135	150
Right knee—circumference (cm.)	37.0	34.5	37.0	35.0
Left knee—circumference (cm.)	36.5	34.0	36.0	34.0
Right ankle—circumference (cm.)	30.0	25.0	30.0	29.0
Left ankle—circumference (cm.)	29.0	26.0	28.0	26.0
Pain	++	0	+++	0

The period of sodium bicarbonate administration was characterized by an increase in body weight and in joint swelling. Joint mobility was significantly decreased and in some instances joints essentially asymptomatic before the onset of these observations became swollen and painful. Pain was aggravated in each case. Case 4, who had had no pain initially, developed severe pains. Case 5 developed more pain while receiving sodium bicarbonate than she had initially.

Discussion. Under the conditions of these experiments, the changes in body weight which were observed can be assumed to

represent mainly either water retention or water loss.[3] It was to be expected, therefore, that the period of ammonium chloride administration should be characterized by a reduction in body weight due to water loss, since the diuretic effect of ammonium chloride has been demonstrated by numerous investigators. Similarly, an increase in body weight following the administration of sodium bicarbonate must be attributed to an increase in the water content of the body. In these cases of rheumatoid arthritis the decrease in body weight and in joint circumference with the administration of ammonium chloride, and the increase in body weight and joint circumference with sodium bicarbonate suggests that the fluid in the joints and in the periarticular tissues, as well as the extracellular fluid volume, is affected by these drugs.

The results of these observations are in general agreement with the observation of Scull and Pemberton[6] that the loss of body water in rheumatoid arthritis is associated with clinical improvement. This would suggest that in rheumatoid arthritis the symptom of joint pain is caused, at least in part, by the swelling of articular and periarticular tissues. Similarly, in the absence of definite bony ankylosis, the immobility of the joints in rheumatoid arthritis may be partly due to this swelling and the pain resulting therefrom. To the extent that this is true, and in the absence of definite joint ankylosis, the reduction of tissue edema may be expected to be associated with clinical improvement of the patient as manifested by relief of pain, decrease in the swelling of the affected joints, and an increase in their range of motion. The fact that these changes are readily reversed with the administration of sodium bicarbonate supports such a view.

Other patients not as carefully studied, and not included in this report, have been tried on this régime and similar changes were not uniformly observed. The response was judged largely on the basis of subjective changes and was not as impressive. Some patients noted no changes at all, some rather insignificant improvement with ammonium chloride, and others were moderately benefited. Sodium bicarbonate administration was more often associated with an increase in the severity of symptoms.

It is not the purpose of this report to recommend ammonium chloride or other diuretics as a therapeutic measure in rheumatoid arthritis. However, the striking clinical changes observed in this small series of patients with alterations in the body water suggest the need of further investigation of the rôle of water in this disease.

Case Reports. Case 1. B. R., a 44-year-old white female, had had rheumatoid arthritis for 10 years. At the time these observations were made she was bedridden because of multiple joint involvement. There was pain on motion of both shoulder joints, pains in both elbows and limitation of motion of the left elbow. Both wrists were painful and swollen. The hands showed interosseous atrophy and fusiform swelling about the metacarpo-phalangeal and the proximal phalangeal joints. There was

extreme pain on motion of the hip joints, more marked on the right. Both knee joints were swollen, painful, and limited in motion. The right ankle was swollen, painful, and limited in its range of motion. Although many of the joints were swollen, there was no evidence of pitting edema.

Roentgen ray revealed slight loss of joint space in both knees with decalcification of the adjacent bone. The other joints showed marked decalcification of the adjacent bones, some loss of joint space, but no ankylosis.

After control joint measurements were made for 4 days, the patient was given 8 gm. ammonium chloride daily for 13 days (Table 1). Her weight decreased 6 kg. Concomitantly with the decrease in weight there occurred a significant increase in range of motion of the right knee, left knee, left elbow and both hips. The circumference of the right knee decreased significantly. The circumference of the left knee was also decreased, although not to such a marked degree. All joint pains were remarkably relieved. There was a decrease in the swelling of the left wrist and an increase in the mobility of this joint. The patient tolerated the ammonium chloride well, and she felt generally improved.

Following the period of ammonium chloride, the patient was given 8 gm. sodium bicarbonate daily for 8 days. The changes in measurements are shown in Table 1. During this time her weight increased 4.1 kg. There was a complete reversal of the changes noted in the preceding period. The circumference of the left knee which had not changed remarkably under the influence of ammonium chloride now increased significantly. Joint pains which had been relieved by ammonium chloride became severe, the patient complained bitterly and required analgesics.

The alternating periods of ammonium chloride and sodium bicarbonate were repeated. Each time the periods of sodium bicarbonate administration were characterized by an increase in body weight, increase in joint circumferences, decrease in joint mobility, and increase in joint pain. On the other hand, the periods of ammonium chloride administration were characterized by a decrease in body weight, decrease in joint circumference, increase in joint mobility, and relief from joint pains.

Case 2. A. B. was a 38-year-old white female whose arthritis was of 1 year's duration. At the time these observations were made she exhibited limited ability to abduct or extend the right shoulder. There was swelling of both knees and both ankles, and although their mobility was not impaired to passive movement, she was unable to walk because of pain and limitation of active motion. The patient required 45 gr. of acetylsalicylic acid daily to control her pain, and she was given codein every night to assure a night's sleep. Roentgen rays of the affected joints revealed no ankylosis and no joint destruction.

The patient was given 8 gm. ammonium chloride daily for 22 days. During this time her weight decreased 5.8 kg. The degree of abduction and extension of the right shoulder were significantly increased. Swelling of the right knee and ankles decreased. Joint pains which had been a prominent symptom previously were completely relieved, analgesics were unnecessary and she was able to walk.

Ammonium chloride was then discontinued and 8 gm. sodium bicarbonate were administered daily for 15 days. The patient's weight increased. The swelling of the knees and ankles returned. Pain promptly reappeared and became even more severe.

The final period of ammonium chloride administration (8 days) was again characterized by a loss of weight, increased mobility of the shoulder, and diminished circumference of both knees. Joint pains were again completely relieved. This patient was sufficiently improved to be discharged to the outpatient department. Table 2 shows the summarized data on this patient.

CASE 3. V. B. was a 28-year-old white female whose illness was of 3 years' duration. At the time of these observations the patient complained of severe pain and stiffness of the cervical, dorsal, and lumbar spine. There was pain and limited abduction of the right shoulder; pain, swelling, and limited motion of the right knee and both ankles; pain, swelling, and fixation at an angle of 90° of the left knee. Roentgen ray examination showed no evidence of bone or joint changes in the cervical, dorsal, or lumbar spine. There was decalcification of the bones of both knees and ankles with sharply etched articular surfaces but no ankylosis.

The patient was given 6 gm. ammonium chloride daily for 26 days. During this time her weight gradually decreased 3.5 kg. The degree of abduction of the right shoulder increased significantly. The range of motion of both knees and ankles increased while the swelling decreased. Pain was remarkably relieved and no medication was needed. Mobility of the spine was not affected although back pain was relieved.

Following this period, 6 gm. sodium bicarbonate were administered daily. As is indicated in Table 2, the patient gained approximately 3.2 kg. in weight. Pain of the joints became a very prominent symptom so that she required codein. The swelling of the joints increased and, in general, the range of motion decreased.

In the final period of ammonium chloride administration the symptoms of pain again disappeared completely. Swelling of the joints decreased. The range of motion of the knees and right shoulder was further increased, and the patient felt considerably better.

CASE 4. I. S. was a 48-year-old white female whose rheumatoid arthritis had become progressively worse over a 10-year period. At the time these observations were made, there was swelling of the dorsal surfaces of both hands and of both knees, although mobility was not markedly impaired. Both ankles were swollen and moved with difficulty. Pain of the joints was not a prominent symptom at this time. Roentgen ray revealed marked narrowing of joint spaces in the left hand and knees.

During a 23-day period of ammonium chloride administration the patient's weight decreased 3.2 kg. The circumferences of the knees and ankles decreased significantly, the puffiness of the dorsal surfaces of the hands disappeared and the mobility of the fingers improved.

During the next 10 days the patient received 8 gm. sodium bicarbonate daily and gained 3 kg. in body weight. The circumference of the affected joints increased to approximately their initial size. Joint pain, which had previously not been a prominent symptom, became severe and the patient required codein for its relief. Swelling of the dorsal surfaces of the hands reappeared and the patient complained of numbness of the fingers of both hands.

During the final period the patient received 8 gm. ammonium chloride daily for 7 days. The weight again decreased. The circumferences of the knees and ankles diminished, and joint pain was relieved.

CASE 5. A. K., a 47-year-old white female, had had rheumatoid arthritis for 8 years. When these studies were begun, she complained of pain and restriction of motion of both shoulder joints, more marked on the right. Both elbows, wrists and knees were swollen, painful and limited in motion. The ankles and toes were deformed and not movable. Analgesics were continually required.

Roentgen ray revealed destruction of many of the joint spaces with bone erosion and decalcification of all the bones.

For 33 days the patient received 8 gm. ammonium chloride daily and lost 1.4 kg. During this period the degree of extension of the right shoulder increased. The circumference of the right and left knees and the right and left ankles decreased without improvement of joint motion. Joint pains were decreased, and no medication was required.

For the next 7 days the patient received 8 gm. sodium bicarbonate daily. During this time she increased her weight 1.2 kg. The degree of extension of the right shoulder was again decreased to its original value. The circumferences of the knees and ankles again were increased. Edema of the face and of the dorsal surfaces of the hands developed. Joint pains became severe and required analgesics for their control.

For the next 6 days the patient again received 8 gm. ammonium chloride daily. Again her weight decreased, and the circumferences of the knees and ankles were decreased. Edema of the face and hands again disappeared. Joint pains were again relieved, and no analgesics were required.

Summary. Five females with typical rheumatoid arthritis were placed on a fixed diet and were given ammonium chloride and sodium bicarbonate while changes in their body water were estimated. With the loss of water induced by ammonium chloride there was in general a decrease in the pains and joint swelling and an increase in the joint mobility. These changes were reversed by the accumulation of water induced by sodium bicarbonate. It would appear that, in these cases at least, some of the symptoms of rheumatoid arthritis are altered to some degree by changes in the body water.

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SALMONELLA INFECTION IN INFANTS AND CHILDREN

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Due to improved feeding techniques and milk control, infantile diarrheas no longer play the rôle they used to do in the earlier years of the century. However gastro-intestinal disturbances are still being observed in single instances as well as in epidemics. The causes of these gastro-intestinal disturbances have been ascribed to overfeeding of good food, to feeding of bad food, to infections in general, and to specific bacterial diseases with their principal symptoms in the intestinal tract. As in other countries, so in the United States, these intestinal cases with a distinct bacterial etiology have seemed to be on the increase, or perhaps we have a better technique in finding the cause. So there are increasing reports of

dysentery, especially of the Flexner type, being published. In addition a whole group of Salmonella (paratyphoid) infections are being brought to light in all countries in the world. This of course is especially important to pediatricians, and it is of this group of cases that we wish to make a short presentation.

Salmonella infections in infants and young children manifest themselves clinically either as diarrheas under the caption of gastro-enteritis, or as bacteremias with or without localization. Occasionally a mixed form is seen. The typhoid type occurring in adults and older children is rather unusual during the first years of life. The gastro-enteric form usually is accompanied by a fever of a non-specific type but not necessarily so. The stools are usually watery, but may be dysenteric in nature. The cases without temperature and with a few watery stools are, of course, very often not recognized. In fact this picture with or without temperature, with or without blood in the stool, can really only be diagnosed by careful bacteriologic examination. Of course, in the young infant the picture of alimentary intoxication may also supervene. The type with bacteremia or marked general infection may have any and all kinds of complications which occur in any bacteremic involvement in the young infant.

To obtain a fairly accurate idea of the rôle played by Salmonella infections in infantile diarrheas in a given locality, 3 factors are of importance. First, awareness of the possibility of such infection in any form of diarrhea in the individual case or in epidemics. Second, consistency in the search for the etiology, which means examining more than just an occasional specimen of the stool; and third, the use of proper laboratory technique consisting of the use of selective media, enrichment procedures, and serologic differentiation. Thus Hormaeche and co-workers,[1] examining stools of 1611 children in Montevideo, found in 395 cholera-like, dysentery-like diarrheas, or transition forms. In this group Shigella organisms were found in 32% and Salmonellas in 20%. Among the other cases with watery stools only, were 85 with Salmonella and 12 with Shigella in the stools. There were furthermore 11 cases with Salmonellas and 3 with Shigellas in the feces with no clinical symptoms whatever. Similar large-scale examinations have not been carried out elsewhere, yet it can be said that aside from possible numerical differences in this country, Salmonella infections are not an infrequent cause of infantile diarrhea.

Present Study. In a series of 369 cases of human Salmonella infections in North America and in Cuba, in which clinical information was available, the types of the organisms were classified by us at the New York Salmonella Center connected with this hospital. Fifty cultures came from infants and young children. The clinical picture was that of a septic infection in 9 cases, and in the remaining 41 children the predominant symptom was diarrhea.

The serologic Salmonella types found in these children were: Group B, *S. typhi murium;* Group C, *S. choleræ suis, S. oranienburg, S. bareilly, S. montevideo, S. newport;* Group D, *S. enteritidis, S. eastbourne;* Group E, *S. give, S. anatum;* Group F, *S. wichita, S. urbana, S. havana,* and *S. panama.* Eleven cases were due to *S. typhi murium* and 25 to organisms belonging in the serologic Group C of Salmonella. These two etiologic groups are the most numerous also among the adults in the series. There, however, *S. typhi murium* occurred twice as often as organisms of Group C. A greater susceptibility of infants and young children to infections with *S. suipestifer,* a representative of Group C, was assumed to exist by Gajzágó and Goettche.[2] This seems to be confirmed by our figures and extended to Group C as a whole.

Eight cases of Salmonella infections observed in our Pediatric Department within the past 3 years present several interesting features. There were 3 cases of simple gastro-enteritis due to *S. typhi murium* involving infants of 3 and 5 months and a 3-year-old child. A 10-year-old boy with enteric fever due to *S. paratyphi B* received sulfaguanidine for 40 days, but the stools were not freed from the organisms. A case of a purulent lesion and 1 of enteric fever due to *S. typhi murium* as well as 2 cases of infant diarrhea due to more unusual types of Salmonella, namely *S. newport* and *S. montevideo,* shall be described briefly.

In our experience, *S. typhi murium* is the most common type found in human Salmonella infections in this country and causes in 9 out of 10 cases a rather harmless gastro-enteritis. *S. newport* and *S. montevideo* represent each about 7% of the human infections in which we have examined the type. Both organisms belong in Group C of Salmonella and show a higher degree of invasiveness in man than *S. typhi murium.* They may cause enteric fever and septic infections aside from gastro-enteritis though not as frequently as *S. paratyphi B* and *S. choleræ suis* respectively.

Case Abstracts. Case 1. M. G., an 11-months-old female (admitted 2/19/39) was operated on 5 weeks before for intussusception; reduction was performed. The child had fever between 101° and 104° for 2 days, was restless and had projectile vomiting 4 to 5 times a day. Three to 4 loose, greenish stools; benzidine test positive. There was a trace of acetone in the urine. Three days after admission the temperature rose to 105.4°. There was slight distention of the abdomen. The following day the abdomen was tympanitic, seemingly tender, there was diffuse resistance, but no masses were felt. A tap in the left lower quadrant revealed pus, from which *S. typhi murium* was cultured. The temperature dropped immediately after the paracentesis and the child was discharged much improved on 3/6/39. At no time were pathogenic organisms found in the feces.

Case 2. A. L., a 5-year-old female (admitted 9/12/41) had fever for a month. During the first week of the fever she had 4 to 5 stools daily; no blood in them. She became afebrile on the second day in the hospital. Stools were examined on 9/12, 9/16 and 9/19 and found negative for pathogenic organisms. An agglutination test with the patient's serum on 9/15

was positive for *Paratyphoid B-O* in dilution 1:200, but negative with the specific phase flagellar antigen of *Paratyphoid B* (*b*). However, a positive agglutination was obtained with the specific phase flagellar antigen of *S. typhi murium* (*i*). The agglutinin titer for *S. typhi murium* in the patient's serum was 1:1600 on 9/20. Only from a stool specimen on 9/24 was *S. typhi murium* finally recovered.

CASE 3. R. S., 2 months old, female, admitted 10/5/40, born in London, had reached this country 2 weeks before; had not gained weight during the last 2 weeks; was emaciated; buttocks excoriated. The stools were mucoid, bloody on one occasion only. *S. newport* was cultured from the stool. After a blood transfusion and dietary treatment, the diarrhea was stopped a week after admission. The patient's serum agglutinated *S. newport* in a dilution 1:200. The mother's serum agglutinated the organism weakly in dilution 1:100. Her stools were negative for pathogenic organisms, she gave no history of enteric infection. Sulfanilamide, 5 gm. in all, sulfanilylguanidine 1.26 gm. per day for 8 days, and sulfathiazole 3.15 gm. did not free the stools from the Salmonella organism. A stool of the child obtained 8 months later, was positive for *S. newport*.

CASE 4. I. E., a 7½-months-old male, was admitted (12/2/40) because of diarrhea, fever and anorexia. He had had an attack of diarrhea 9 days before, which subsided within 4 days. The stool contained *S. montevideo*. Patient's serum agglutinated the organism in dilution 1:50. The stools were loose, contained specks of blood, became normal on the 5th day in the hospital. Sulfanilylguanidine was given for 12 days, stool cultures were still positive on discharge 12/21/40.

CASE 5. S. B., a 3-year-old male, was admitted (2/7/39) for cough and discharge from nose, for 1 week, temperature between 100° and 103.5°. Since 5 days, 6 to 10 loose yellowish-green stools—abdominal pain and vomiting. *S. typhi murium* was isolated from the stool, the patient's serum agglutinated this organism up to dilution 1:200. The temperature came down to normal on the 2nd day in the hospital, from the 3rd day on the child had 2 to 3 pasty brown stools.

CASE 6. E. L., a 5-month-old male, was admitted 2/13/39. The child had fever, cough and ear discharge for 6 weeks. Febrile temperature since 2 weeks; 6 to 8 watery stools within the last 24 hours. During the first 3 days in the hospital he had 4 to 5 loose yellow stools a day; on one occasion the feces were blood-streaked. *S. typhi murium* was found repeatedly in the stools; agglutination test with the patient's serum on 2/20/39 was negative.

CASE 7. N. L., a 3-month-old male, was admitted (10/6/39) because of fever and diarrhea for 5 days. Acutely ill, dry skin, hollow eyes. Bright red bloody stools. Clinical impression: dysentery. *S. typhi murium* in feces.

CASE 8. H. M., a 10-year-old male, was admitted 9/20/41; a refugee child; infected on a Spanish boat, had periumbilical pain and fever up to 104° for 3 days; constipation, anorexia. Spleen 1 finger below costal margin, few rose spots on 9/23. Septic temperatures—gradually decreasing until 12th day in hospital. *S. paratyphi B* from blood and stool. Agglutination with *S. paratyphi B* rose up to 1:1600. Sulfaguanidine for 40 days, positive stool cultures were obtained after discontinuation of the drug.

It is known that Salmonella infections tend to occur during the summer months. Yet none of these 8 cases fell into this season. No connection with other cases or carriers could be detected except for the case R. S., whose mother possibly had a subclinical infection. Contrary to the statements of most authors, a carrier state was

observed for a considerable length of time. It may be noted that the therapeutic use of sulfanilylguanidine proved ineffective in Salmonella infections not due to *S. paratyphi A* or *S. choleræ suis*.[2]

Summary. Routine cultural examination of a series of stool specimens from all infants and children with gastro-intestinal symptoms is suggested. Agglutination tests are not without value, although they are not always positive in cases of simple gastro-enteritis. According to Hormaeche they become positive more often in the dysentery-like cases than in other forms of enteritis. Nevertheless, in all doubtful infections of more than a week's duration, agglutination tests with a variety of Salmonella antigens should not be omitted. Blood cultures should also be taken if the syndrome is that of enteric fever or generalized septic infection.

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CYANIDE POISONING FROM CHOKE CHERRY SEED

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In these western states, the numerous choke cherry trees yield berries, the pulp of which is used by some for jam-making and eaten raw in large quantities by campers—Indian and white alike. In instances where there exist great hunger or an injudicious appetite or craving, the fruit may be eaten whole, or the seed and pulp broken up in the mouth and swallowed indiscriminately.

The fresh pits of the choke cherry, *Prunus melanocarpa*, contain enough cyanide to be poisonous, perhaps lethal, to the consumer. This property is shared by the fresh pits of peach, prune, and several other similar plants.[3] Among western Indians the choke cherry is an important dietary item during the months of August and September.

Although it is well known that the fresh peach seed is poisonous, very little attention has been given to the seeds of the wild choke cherry. A thorough search of the literature reveals but one publication on the subject. In Pardee's[3] case (1847) certain singular features of his patient bear repetition: "A little boy about three years old had been in the habit, in the fall of 1846, of resorting with other boys to a tree of the wild choke cherry and of eating freely, and at all times, of the choke cherries, the tree being of easy access and being loaded with fruit, and the ground underneath being well covered with them. He seemed to have swallowed great numbers of them whole. One morning, while apparently in the enjoyment

of his usual health, he began to complain of pain in the epigastric region and soon after vomited and discharged quantities of whole cherries; he had convulsions, was drawn backwards, rolled his eyes about, and died in a short time, before any medical aid reached him. I made a postmortem examination on the day subsequent to his death and found, on opening the abdomen, that the stomach and intestines were of a dark, modena red color, such as would be caused by the juice of the wild cherry infiltrating through the walls of stomach and intestines. And on opening the alimentary canal, I found it literally filled with cherries in every condition—indeed, there were at least two quarts of cherries in the whole alimentary canal."

Case Abstracts. CASE 1. Unfortunately, this case reported by Pardee was unknown to me when, in August of 1940, a 14 year old Indian school girl was admitted to the Western Shoshone Hospital. She was stuporous, had intermittent attacks of convulsions non-Jacksonian in character, was pale, cyanotic, her respirations labored, and a rectal temperature of 105°.

Physical examination revealed no contributory neurologic signs. There were equivocal Babinski reactions, but no Oppenheim or Gordon signs. The pupils were equal and reacted to light and accommodation. Although rolling of the eyeballs was present, the eyes presented no fixed deviation. Inability to coöperate prevented other neurologic studies. The chest was normal to percussion and auscultation, confirmed by a roentgenogram (Roentgen ray plates of the skull were normal), and a *KB* film of the abdomen revealed certain small circumscribed shadows, the interpretation of which was uncertain. The cerebrospinal fluid showed no abnormality, although the pressure was low.

The blood studies presented a white count of 14,200 (differential negative); red blood cell count of 2,800,000. The venous blood seemed to have a slight vermilion hue. There was a slight increase in the venous pressure (140 mm.); systolic arterial pressure, 76 mm. Hg; diastolic, 30. The pulse rate was 140; the heart sounds muffled, but well heard. The urine (by catheterization) was entirely negative, no acetone, acetoacetic acid, sugar, albumin, or microscopic abnormalities. The abdomen was soft, and there were no muscle responses to pressure palpation. Rectal examination was negative.

A continuous intravenous drip of 5% dextrose on Hartman's solution was started and no other form of treatment used. The patient died in 24 hours.

Autopsy (limited to the gastro-intestinal tract) revealed large quantities of choke cherries and broken seeds throughout the tract. The entire mucosa was deeply stained red by the cherries themselves. There was nothing else abnormal found in the gastro-intestinal system.

Inquiry disclosed that the patient had spent several days in the mountains, subsisting mainly on choke cherries,[1] and, apparently, in her hunger, had eaten huge quantities of cherries, in many instances breaking the seeds in her mouth. This point is stressed, as the ingestion of the broken fresh seeds is of paramount importance clinically.

E. V. A. Murphy, a visiting botanist, made the suggestion that members of the family rosaceæ, which includes choke cherries, contain seeds whose pits are poisonous and confirmed our impression that the choke cherry, like other members of this family, might produce hydrocyanic acid. It is well known[1] that cherry, almond, and peach seeds and leaves contain cyanophoric glucosides.

Fresh choke cherries were obtained and the pits removed, crushed and given to 3 guinea pigs. All of these animals died in convulsions. Here, then, was a poisonous substance at least lethal to guinea pigs, 2 gm. sufficing to produce death. The pits of seeds were then crushed, distilled in acid and the distillate absorbed in weak base. The distillate absorption (0.1 cc.) was lethal to guinea pigs within 8 minutes. Qualitative tests for cyanide were strongly positive. Lack of facilities rendered further assay impossible. It was apparent that this substance could be liberated from choke cherry seeds during acid hydrolysis in the stomach. Dried crushed seeds exposed to air apparently lost their toxic properties.

Numerous reports in the literature[2] indicate that the equivalent of 60 mg. of hydrocyanic acid may be fatal, but larger doses have been recovered from. The longer the patient is kept alive, the better his chances are for recovery, because the body detoxifies cyanide by combining it with methemoglobin and sulfur compounds to form stable and inactive sulphocyanates.

While it is true that cyanide combines with hemoglobin to form cyanhemoglobin, a non-oxygen bearing compound, this substance is formed slowly and in a small amount. Death is not due, primarily, to cyanhemoglobin or to a cyanide effect on the carotid sinus, but to its inhibition of cell respiration; the respiratory center in the medulla ceases to function because its nerve cells can no longer obtain oxygen for its respiration. Even though the blood is saturated with oxygen, the tissues are incapable of utilizing it.

Now, as the breakdown of cyanogenetic glucosides, of which the choke cherry amygdalin is one, is a slow process in the gastro-intestinal tract, and as cyanhemoglobin is formed slowly, the treatment is directed along two channels: first, to cease ingestion of toxic material and, secondly, to remove all material already ingested from the gastro-intestinal tract.

Methylene blue is of no value therapeutically, and under some circumstances it can even hasten the reconversion of methemoglobin, a useful compound forming a stable substance with cyanide, to hemoglobin. Sodium thiosulphate and sodium nitrate are the safest agents to employ for methemoglobin formation in cyanide poisoning. However, these measures with occasional side toxic reactions are unnecessary if the cyanide-producing material is removed from the individual. This is demonstrated by the fact that 3 other cases were admitted during September, 1940, with symptoms of coma, convulsions, vasomotor collapse, labored respirations not of the Küssmaul type but more of a Cheyne-Stokes character, the skin having a suggestive pink cyanosis. Vomiting and epigastric pain were the early symptoms in all these cases. Treatment consisted of gastric lavage with weak sodium bicarbonate solution, repeated high enemata and the subsequent administration of 15% magnesium sulphate solution in large quantities through a Levine tube placed well into the duodenum. Lumbar punctures

were done in each case with a beneficial effect. Intravenous dextrose solutions and small transfusions were also helpful.

TABLE 1.—DATA ON 4 CASES OF CHOKE CHERRY SEED POISONING

Name	Age	Date	Admission temperature	Central nervous system	Neuromuscular system	Vomiting as early symptom	Blood in G-I. contents	Treatment	Result
H. D.	12	8-24-40	105	Deep coma convulsions	Fibrillary muscular twitchings	+	+	None	Died
H. R.	15	8-30-40	101[2]	Stupor, cannot talk; semi-comatose	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.
P. T.	54	9- 2-40	100	Slight stupor, listless, barely able to talk	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.
C. R.	14	9-10-40	98[4]	Partial coma dizziness barely able to talk	Fibrillary muscular twitchings	+	+	Removal of seeds	Complete recovery in 24 hrs.

In these 3 cases the diagnosis would have been missed, the treatment ineffective and death unquestionably would have occurred, had we not ascertained the direct cause of the symptoms. There have probably been mild cases of choke cherry seed poisoning, the symptoms of which must have bewildered the physician. It is only by the ingestion of fresh crushed seeds that a toxemia is induced.

Conclusions. Four cases of poisoning from the ingested, fresh seed of the western choke cherry, *Prunus melanocarpa*, are presented. The fresh pit of this western choke cherry is said to contain cyanophoric glucosides which break down into hydrogen cyanide in the gastro-intestinal tract, producing hydrocyanide poisoning, which may be fatal. The treatment for this type of cyanide poisoning is also presented.

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THE EFFECT OF BENZEDRINE SULFATE IN MIGRAINE*

A PRELIMINARY REPORT

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THE purpose of this report is to describe the effectiveness of benzedrine sulfate† (amphetamine sulfate or beta-aminopropyl-

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† Benzedrine sulfate prepared for intravenous administration was kindly supplied by the Smith, Kline & French Laboratories, Philadelphia, Pa.

benzene sulfate) in the treatment of migraine. The results indicate that this drug may be a useful addition to the physicians' armamentarium for the treatment of this disease.

Regardless of the basic pathogenesis of migraine, evidence accumulated to the present time implicates a local disturbance of the arterial system, angiospasm or dilatation, as the immediate causal agent for a paroxysm. The studies of Wolff and his associates[1] indicate that dilatation and distention of cranial arteries which may be produced by a variety of factors form the basis of the headache. The effectiveness of ergotamine tartrate in adequate dosage in aborting, reducing or terminating an attack of migraine headache has been demonstrated consistently since its introduction by Lennox and von Storch in 1935.[2] This drug decreases the amplitude of the pulsations of the cranial arteries, chiefly certain branches of the external carotid artery.[5] Its therapeutic effect depends presumably on its ability to produce prolonged and powerful vasoconstriction.

Unfortunately following the administration of ergotamine tartrate undesirable symptoms of a toxic nature frequently occur. Von Storch[6] has discussed the limitations of this therapy. The commonest untoward reactions were nausea, vomiting, numbness and tingling of the hands and feet, muscular pains and muscular stiffness. These, if severe and prolonged, besides being decidedly unpleasant to the patient, may constitute a warning of impending arterial thrombosis. Other symptoms such as insomnia, restlessness, globus hystericus, choking sensations and precordial pain occur less frequently and, although alarming to the patient, do not seem dangerous. The occurrence of any of these accessory symptoms whether dangerous or not may be of such importance to the patient as to prevent the use of the drug for therapeutic purposes.

As a result a study was begun with the purpose of evaluating benzedrine sulfate as a possible therapeutic agent. This drug was selected because it is a sympathomimetic compound with a prolonged action. Vasoconstriction with its concomitant pressor effects was desired. It too decreases the amplitude of the pulsations of the cranial arteries.[5] The increase in psychic function with a lessening of fatigue which this drug produces was thought possibly to be of value because slowness of thought and fatigue are frequently a part of the migraine syndrome. This drug can also produce undesirable reactions such as intense restlessness, inability to relax, insomnia and cardiac irregularity, depending upon individual idiosyncrasy. It is contraindicated for patients with cardiovascular disease, particularly those with hypertension. It must, therefore, be administered with due caution.

Benzedrine sulfate has been given previously to patients suffering from migraine, but not studied extensively. Nathanson[3] in a study of the effects of benzedrine sulfate on fatigue had 4 subjects in his

series who complained of migraine attacks when they became easily tired. He was administering the drug orally in 10 mg. doses before breakfast and at noon. He found that the frequency of their migraine attacks lessened with amelioration of fatigue. In addition 1 patient was able to prevent the headache by taking 10 mg. by mouth during the prodromal stage. Palmer[4] found it of no value in 3 cases. Sutherland and Wolff[5] observed that an intramuscular injection of 10 mg. was sufficient to relieve the attack in 1 of 3 cases. Collectively then 10 patients have been reported as receiving this drug for their migraine. Two obtained relief from attacks, 3 others had the frequency of their attacks reduced while the remaining 5 were unaffected.

Procedure. Twenty-five patients suffering from typical migraine but free from other discernible disease form the basis for this study. If the patients reported to the hospital during an attack, the drug was administered intravenously in 3 to 20 mg. doses. The rate of injection was given cautiously, 1 mg. per minute for the first injection. Subsequently, if no untoward symptoms developed, the speed of injection was increased, reaching a maximum in 1 patient of 20 mg. in 3 minutes. The speed of injection was controlled according to the rise in blood pressure which was taken at minute intervals. An increase of 20 to 40 mm. Hg in the systolic blood pressure was used as the criterion. There was great variability among the patients in their sensitivity to the drug—the blood pressure arose abruptly in 2 patients after administration of but 3 mg. and 7 mg. intravenously. The injections were then discontinued because they were deemed dangerous.

Following testing of their response to intravenous medication, these patients were advised to take the drug orally in 10 to 40 mg. doses at the beginning of an attack. Seven patients who were examined between attacks were placed directly on oral medication. Three patients having very frequent and severe paroxysms were placed on oral medication daily at varying intervals up to every 4 hours in order to evaluate the drug as a prophylactic agent.

Results. The accompanying table presents the results and types of medication employed for the treatment of 25 patients suffering from migraine. Eighteen of these patients received benzedrine sulfate intravenously from 1 to 7 times for the relief of their migraine attacks. Twelve (67%) consistently obtained complete relief from their attacks in from 7 to 45 minutes. All of them were suffering in their attack near or at its height. The rapid disappearance of the symptoms was dramatic and startling. Most of the attacks were exceedingly severe with confusion being prominent in 3; 9 had complete relief of all symptoms; 2 usually had residual hyperesthesia over the affected side which gradually disappeared during the following 2 hours; and 1 usually had a dull residual lasting several hours which gradually faded away. Three of these 12 on some occasions had a recurrence of their symptoms after 4 hours. These subsequent symptoms were relieved by further intravenous administrations. Of the 6 patients who failed to obtain relief, 2 obtained relief regularly from ergotamine tartrate, 1 from oxygen therapy, but the other 3 failed to respond to any therapy employed.

TABLE 1.—SYMPTOMS, TYPES OF MEDICATION EMPLOYED AND RESULTS OBTAINED IN THE SYMPTOMATIC TREATMENT OF 25 PATIENTS SUFFERING FROM MIGRAINE

		Symptoms				Benzedrine sulphate				Ergotamine tartrate				
	Case No.	Headache	Scotomata	Nausea and vomiting	F.H.	Intravenous (mg.)	Relief	Oral (mg.)	Relief	Intravenous (mg.)	Relief	Oral (mg.)	Relief	Oxygen, relief
1	4	Hemicrania	0	0	0	10	In 30″	10–20	In 30–60″					
2	6	Hemicrania	0	0	0	3–10	" 10–15″	10	" 60″					
3	8	Hemicrania	+	+	0	6–10	" 10–15″	10	" 45″					
4	1	Hemicrania	+	+	+	10	In 15–60″	10–20	None	0.5	In 30″	5.0	None	Partial
5	7	Hemicrania	+	+	0	10	" 15″	10	"					
6	12	Hemicrania	+	+	+	10	" 15–30″	10–20	" tox.	..	..	3–5	None	
7	16	Bilateral	+	+	+	10–20	" 30–45″	20–40	"	0.5	None	5.0	"	None
8	18	Hemicrania	+	+	+	10	" 30″	10	" tox.	0.25	In 30″ tox.	..	..	"
9	19	Hemicrania	0	+	+	20	" 7–25″	10–20	"					
10	17	Bilateral	0	+	+	10	" 15″							
11	21	Hemicrania	0	+	+	10	" 35″							
12	23	Bilateral	+	+	+	10	" 10″							
13	5	Bilateral	+	0	0	10	None	10–20	"	0.5	None tox.	..	..	"
14	9	Bilateral	+	+	0	10	"	10–20	"	0.25	In 30″	5.0	In 60″	
15	10	Bilateral	+	+	+	10	"	10	"	0.25	" 30″	2.0	" 60″	
16	22	Hemicrania	0	+	+	20	"	10–20	"	0.25	None	..	..	"
17	24	Bilateral	+	+	+	20	"	10	"					
18	25	Hemicrania	+	+	+	7	"	10–20	"	0.5	"	..	..	In 60″
19	2	Bilateral	+	+	+	..	..	10–30	In 30–60″					
20	3	Hemicrania	+	0	0	..	..	10	" 30″					
21	14	Hemicrania	0	+	0	..	..	10	" 60″					
22	15	Hemicrania	0	0	+	..	..	10–20	" 30–60″					
23	20	Hemicrania	0	+	+	..	..	10	" 30″					
24	11	Bilateral	0	0	+	..	..	10–20	None	..	..	2.0	" 30″	
25	13	Hemicrania	+	+	+	..	..	10	" tox.	0.25	None	..	..	None

The injection of benzedrine sulfate intravenously was approached with due caution. In our experience with complete control over the dosage there has been no serious reactions. The accompanying physiologic changes were fairly consistent qualitatively from patient to patient. There was an increase in the blood pressure of 15 to 40 mm. Hg in both the systolic and diastolic pressures which reached their maxima in 5 to 10 minutes after the injections were completed. An increase in blood pressure was found necessary in order to obtain relief and the rate of injection was controlled by the rise in blood pressure. The pressures then slowly fell until the original level was reached in 45 to 60 minutes. The pulse rate varied, increasing on some occasions but more commonly diminishing from 8 to 15 beats per minute at the height of the reaction. Pallor was common. Slight dilatation of the pupils occurred. Only 4 complained of feeling tense to the point where it was uncomfortable. Most of the patients remarked that they felt brighter and no longer fatigued. Insomnia, which had been anticipated as a possible complication did not occur and presented no particular problem. One patient reported greater ease in breathing as his nasal passages felt clear. Another stated his chest felt heavy and breathing was difficult. The most serious complication was a cardiac irregularity characterized by extrasystoles. This disappeared in 40 minutes. All symptoms of stimulation of the central and autonomic nervous systems had completely disappeared in 60 to 90 minutes. So in summary then there was only one possible serious toxic reaction—the cardiac irregularity out of a total of 51 intravenous injections. In the majority the reactions were so mild that discomfort was minimal.

As indicated in the accompanying table, 22 patients were given benzedrine sulfate to take by mouth in prescribed doses of 10 to 40 mg. at the onset of a migraine attack. Medication administered orally was not as successful as when given intravenously. Eight patients (36%) of the group obtained relief or had their paroxysms aborted in 30 to 60 minutes. In no case was oral medication effective, if the desired reaction could not be obtained by intravenous administration. In comparing quantitatively the severity of the paroxysms of the patients, it became apparent that those patients who obtained relief by oral medication suffered from typical but mild attacks. These patients reported a difference in their subjective response to the drug, depending upon whether it was taken at the time of an attack or on some other occasion. If taken during a paroxysm, toxic symptoms such as tension, restlessness, increased energy output and insomnia were usually less severe than on other occasions.

In contrast to the patients with mild and infrequent paroxysms were 3 cases at the opposite end of the scale, having frequent and severe attacks. They responded well to benzedrine sulfate when it

was given intravenously. The frequency of their paroxysms, however, was such a serious problem that it was decided to try the drug as a prophylactic agent. Small oral doses were administered frequently during the day in 2 cases and during the day and night in the third. A maintenance dose was found for each one of these patients which relieved them of their paroxysms, yet was not sufficient to cause toxic manifestations.

The most interesting patient from this viewpoint may be briefly presented:

CASE 1. She was a 34 year old married woman admitted to the hospital on May 16, 1941, because of severe migraine characterized by left-sided headaches, scotomata, nausea, vomiting and confusion occurring every 2 to 3 days. Of interest was the fact that her father, mother, 2 paternal aunts and 2 sisters suffered from typical migraine. In this patient those attacks had been present for many years and had completely incapacitated her for the preceding 11 years following the birth of her only child. The attacks could be controlled only by tremendous amounts of morphine and its derivatives or barbital and its related compounds. For example, the day before admission she had been given 1 gr. morphine, 1 gr. pantopon and 12 gr. phenobarbital. Following admission, there was a prolonged severe reaction due to withdrawal of these drugs. After recovery from this, she began to have frequent severe paroxysms almost daily and was completely incapacitated. She was refractory to ergotamine tartrate as well as various analgesics and salicylates, but responded promptly to benzedrine sulfate when administered intravenously in 20 mg. doses. This large amount was necessary not only to relieve the individual attack but also to cause a blood pressure rise. She was then placed on oral medication in 10 mg. doses every 4 hours. At first the drug was taken at 6 A.M. and 10 A.M. Paroxysms then occurred only in the afternoons. The medication was then extended to 2 P.M. and 6 P.M. with the attacks then occurring during the night. Epinephrine in oil (2 cc.) was then added and injected intramuscularly at 10 P.M. resulting in complete relief for the patient. Finally benzedrine sulfate was substituted for the epinephrine, so that the total medication the patient was taking consisted of 10 mg. at 6 A.M., 10 A.M., 2 P.M. and 7.5 mg. at 6 P.M., 10 P.M. and 2 A.M. On this regime the patient has remained symptom-free. She has become a lively, enthusiastic woman able to resume her life in society which for the preceding 11 years she had been unable to do. She has had only one period of return of her severe paroxysms. This occurred when she exhausted her supply of medication and there was a delay in the replenishing of it.

Summary and Conclusions. Twenty-five patients suffering from migraine were treated symptomatically with benzedrine sulfate. Twelve of 18 patients (67%) had their attacks aborted quickly when the drug was administered intravenously. Eight of 22 patients (36%) obtained relief or had their paroxysms aborted when the drug was taken orally during the prodromal stage. Three patients having frequent and severe attacks became symptom-free when the drug was taken daily and in divided doses.

This evidence seems to indicate that benzedrine sulfate is useful in the treatment of migraine. It may be used as a substitute for ergotamine tartrate when the latter is either ineffective or productive

of severe toxic symptoms. It may be administered by mouth daily in repeated small amounts as a means of preventing attacks in those patients suffering from frequent and severe paroxysms.

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HYPOGLYCEMIA FOLLOWING ALCOHOLIC INTOXICATION

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In the past few years, we have seen a number of patients brought to the hospital in a state of hypoglycemic coma following alcoholic intoxication. It has been suspected that these patients had been drinking a denatured alcohol solvent sold locally under the name of "Solox," but in no instance has this been proved. Recently, Brown and Harvey[3] reported the occurrence of hypoglycemia in drinkers of "smoke," a solvent identical in composition with "Solox." The clinical features of our cases have been similar in all respects to those reported by these authors. We have been unable to find any other account of this condition in the literature.

The recognition of this occasional cause of unconsciousness would appear to be a matter of importance. In our cases, treatment with glucose solution intravenously has resulted in rapid recovery. We think that death might readily occur in an untreated patient.

We have been able to add little to the observations of Brown and Harvey as to the cause of this type of hypoglycemia. In the hope that the condition may be more widely recognized and further light thrown on the nature of the disturbed metabolism, the following 4 cases are reported:

Case Reports. Case 1. E. L., a white man, aged 33, was admitted to Memorial Hospital on December 31, 1936, unconscious and having convulsions. He had been drinking bootleg whisky for an indefinite time, and was known to have had several drinks before retiring at 9 A.M. the morning before admission. He had awakened at 7 P.M., and complained of feeling badly. In a short while he became unconscious. He was examined by a physician who found him relaxed, and thought him drunk. Shortly afterwards he began to have convulsions, was seen again by his physician, and sent to the hospital at 1 A.M.

On admission, the patient was completely unconscious, and having frequent tonic convulsions with opisthotonus. The pulse rate was 180, respirations were stertorous with a rate of 42, temperature 100.6° F (rectal), blood pressure 146 systolic, 68 diastolic. The pupils were dilated, but reacted to light. The neck was not stiff between convulsions. The extremities were flaccid between convulsions, and no tendon reflexes were obtained. The remainder of the examination was negative.

Urinalysis showed a specific gravity of 1.022, 2+ albumin, negative sugar, and positive acetone. There were occasional white and red cells, and many hyaline and granular casts in the urinary sediment. Blood counts showed 4.9 million erythrocytes, 96% hemoglobin, 20,000 leukocytes with 88% neutrophils, 8% lymphocytes and 4% monocytes. The blood sugar was 25 mg. per 100 cc., the non-protein nitrogen 50 mg. per 100 cc. The Kline test was negative.

It was at first thought that the patient might have strychnine poisoning. Gastric lavage was done, and large doses of sodium phenobarbital given hypodermically. This resulted in complete relaxation. Lumbar puncture revealed a clear fluid under 160 mm. pressure, containing 3 cells. When the report of the low blood sugar was obtained, 50 cc. of 50% glucose solution were given intravenously. Within a few minutes, the patient regained consciousness and asked for whisky. He remained conscious, and was able to take a liquid diet the following day. The blood sugar the morning after admission had risen to 224 mg. per 100 cc. His further course was uneventful, some sedation being given for restlessness. He was discharged on January 2, 1937.

Case 2.—E. B., a negress, aged 35, was admitted to St. Philip Hospital on November 8, 1938, unconscious. She was known to have been a heavy drinker for many years, and 1 year previously had spent several months in a mental hospital. The reason for her commitment was not known. When seen, she was said to have been drinking for 4 days. She had been asleep off and on for 24 hours, and 4 hours before admission had become completely comatose, and could not be aroused at all.

The patient was of a very small stature and slight build (height 4 feet 7½ inches, weight 88 pounds). She was unconscious on admission, but roused slightly to painful stimuli. The temperature was 100.2° F. (rectal), pulse rate 110, respiratory rate 22; blood pressure, 125 systolic, 80 diastolic. The pupils were equal and reacted normally to light. The neck was not stiff. All extremities were held in rigid extension. The tendon reflexes were symmetrically hyperactive, and sustained ankle clonus and positive Babinski reflex were present bilaterally. The remainder of the examination was negative.

Urinalysis was entirely negative, including a negative test for acetone. Blood counts showed 5 million erythrocytes, 95% hemoglobin, 13,800 leukocytes with 73% neutrophils, 23% lymphocytes, 4% monocytes. The blood sugar was 20 mg. per 100 cc., the non-protein nitrogen 23 mg. per 100 cc. Blood Kline and Wassermann tests were positive.

Subarachnoid hemorrhage, or some other form of cerebral accident was suspected. A lumbar puncture revealed a clear spinal fluid which contained 14 cells, 6 neutrophils and 8 lymphocytes. Wassermann and mastic tests were negative. Hypoglycemia was not suspected until the low blood sugar was reported 2 hours after admission; then, 30 cc. of 50% glucose solution were given. The patient soon woke up in a rage. She talked at random all night, but was able to take liquids. The following morning, the blood sugar was again low, 56 mg. per 100 cc., and 2 days later 51 mg. The patient's mental status improved slowly. Two days after admission, she appeared to be entirely rational and otherwise well, and remained so.

Glucose tolerance tests (100 gm. of glucose by mouth) showed the following results: On November 11, 3 days after admission: 60 mg. (fasting),

116, 123 and 122 mg., in ½, 1 and 2 hours respectively; on November 16: 74 mg. (fasting), 89, 70, 84, 80 and 73 mg., in ½, 1, 2, 3 and 4 hours respectively; on November 21: 66 mg. (fasting), 70, 64, 50, 60, 60 and 64 mg., in ½, 1, 2, 4, 5 and 6 hours respectively.

Roentgen ray of the skull showed the sella turcica to be normal, and the pineal body to be calcified and not shifted. On November 22 the basal metabolic rate was −25%. At this time the serum cholesterol was 210 mg. per 100 cc.

The patient was placed on desiccated thyroid, U.S.P., 2 gr. 3 times daily. She was discharged on November 26, to be followed in the out-patient department, but failed to return.

CASE 3.—J. D., a negro barber, aged 33, was first admitted to St. Philip Hospital on July 31, 1939, unconscious. He was known to be a chronic alcoholic, and was said to have been hospitalized elsewhere 1 year before for delirium tremens. He had begun drinking the day before admission, and had returned home at 1 P.M. the day of admission and gone to bed. At 7 P.M. his wife could not arouse him. He had remained comatose until brought to the hospital at 10 P.M. There had been no previous episodes of unconsciousness.

When seen, the patient was in profound coma, not responding to any stimuli. The temperature was 97° F. (rectal), pulse rate 68, respiratory rate 18, and blood pressure 140 systolic, 90 diastolic. The pupils were small, equal and reacted to light. The fundi were normal. The neck was not stiff. There were scattered rhonchi throughout the lungs. The extremities were flexible, but the tendon reflexes were uniformly hyperactive. A questionable Babinski reaction was present bilaterally. There was no ankle clonus. The nails of the fingers and toes were clubbed. The remainder of the examination was negative.

Urinalysis was negative except for a trace of acetone. Blood counts showed 4.4 million erythrocytes, 85% hemoglobin, 5200 leukocytes (66% neutrophils, 32% lymphocytes and 2% monocytes). The blood sugar was 25 mg. per 100 cc., the blood non-protein nitrogen 39 mg. per 100 cc. The Kline test was negative. Lumbar puncture revealed a clear spinal fluid under 80 mm. of pressure. There were no cells, and the spinal fluid Wassermann test was negative.

Hypoglycemia was suspected, and an intravenous infusion of 10% glucose solution was begun. The patient regained consciousness within a few minutes, and seemed fairly rational. He was given high carbohydrate liquid feedings, and remained fairly well until the second day when delirium tremens developed. This was controlled with large doses of barbiturates. The fasting blood sugar on the second day was 113 mg. per 100 cc. Glucose tolerance test (100 gm. of glucose by mouth) 1 week after admission showed the following blood sugar levels: 96 mg. (fasting), 91, 142, 105 and 57 mg. in ½, 1, 2 and 4 hours respectively.

The liver edge, which had not been felt on admission, was subsequently found to be palpable 5 cm. below the right costal margin. No cause was found for the clubbing of the nails, which was stated to have been present since birth. The patient was discharged on August 19, 1939.

On November 16, 1940, 15 months later, the patient was again brought to the hospital unconscious. He had been found in this state in the hall of his rooming house. His wife had been separated from him for a year, and knew nothing of his recent activities. The patient subsequently stated that he had been drinking heavily for 4 months. The last thing he remembered was speaking to a friend in the rooming house about 12 hours before he was brought to the hospital. He could not remember when he had eaten last.

The patient was completely unconscious and ice cold. The temperature was not recorded; the pulse was irregular and feeble, with a rate of 86.

The blood pressure could not be obtained. The respiratory rate was 24. Both pupils were pinpoint, and did not react. The neck was not stiff. The lungs were clear, and the heart was not remarkable except for the irregular rhythm. The abdomen was held rigid. There was rigid spasticity of all extremities, with fine generalized convulsive tremors at times. The tendon reflexes at first could not be elicited because of spasticity, later they were uniformly hyperactive. The plantar reflexes were completely absent. The nails were clubbed.

Urinalysis was entirely negative, including a negative test for acetone. The blood counts were entirely normal. Blood taken at the time of admission showed blood sugar 32 mg. per 100 cc., blood non-protein nitrogen 36 mg. per 100 cc., total serum cholesterol 192 mg., esterified cholesterol 156 mg., and free cholesterol 36 mg. per 100 cc. The Kline test was negative.

Hot water bottles and blankets were applied to the patient's body, and, because of the previous history of hypoglycemia, 50 cc. of 50% glucose solution were given intravenously as soon as blood for chemistry had been drawn. The patient regained consciousness within a few minutes, and was able to take liquid nourishment. He remained rational thereafter. The fasting blood sugar level on the second day was 103 mg. per 100 cc.

After 3 days on a high carbohydrate diet, glucose tolerance test (50 gm. of glucose by mouth) showed the following blood sugar values: 101 mg. (fasting), 150, 156, 82, 87 and 89 mg. in ½, 1, 2, 3 and 4 hours respectively.

Three days after admission, the patient complained of peculiar sensations and coldness in his feet. There was found to be a generalized hyperesthesia of both feet and ankles. The tendon reflexes were still hyperactive. A deficiency neuritis was suspected, and large doses of thiamin chloride were given parenterally, with gradual improvement in these symptoms. An electrocardiogram before thiamin was begun showed slight elevation of St_1 and St_2 with low voltage of all T waves.

Subsequent glucose tolerance tests were done (100 gm. of glucose by mouth). On November 29, the blood sugar levels were 95 mg. (fasting), 124, 130, 106, 74, 55 and 98 mg. in ½, 1, 2, 3, 4 and 5 hours respectively. On December 10, the levels were 88 mg. (fasting), 122, 110, 110, 50 and 65 mg. in ½, 1, 2, 3, 4 and 5 hours respectively.

In an attempt to demonstrate evidence of liver disease, other studies were undertaken. These were done, however, after several days on a high carbohydrate diet, and after thiamin had been given. The icteric index was 8 units. The serum phospholipids were 8 mg. per 100 cc. The oral hippuric acid excretion test[8] (6 gm. of sodium benzoate by mouth) showed excretion of 3.2 gm. of hippuric acid in 4 hours. The intravenous hippuric acid excretion test[7] (1.77 gm. of sodium benzoate intravenously) showed excretion of 1.28 gm. of hippuric acid in 1 hour. These results are not indicative of liver damage.

A Roentgen ray of the skull showed a normal sella turcica, and no other abnormalities. The basal metabolic rate was −6%.

The patient's further course was marked only by a respiratory infection. He was discharged on December 10, 1940.

Case 4. H. J., a negro aged 41, was admitted to St. Philip Hospital on August 21, 1941, unconscious. He was a known chronic alcoholic. Subsequently it was learned that he had consumed a large quantity of whisky on the day before admission. He retired at midnight and arose at 6.30 A.M. the day of admission, and ate one sausage and a biscuit. His last recollection was of setting out for work. He was found unconscious on the street, and brought to the hospital at 8.45 A.M.

When seen, the patient was completely unconscious. The skin was cold but dry. Respirations were shallow with a rate of 15. The pulse was feeble and had a rate of 88. The temperature was 95.6° F. (rectal), and

the blood pressure 150 systolic, 100 diastolic. The pupils were constricted and equal. There was a slow side-to-side conjugate movement of the eyes. The lungs were filled with rhonchi. The extremities were flaccid, no tendon reflexes were elicited, and no pathologic reflexes were present.

Urinalysis was negative except for a 2+ acetone. The blood counts were not remarkable. The blood sugar on admission was 38 mg. per 100 cc., the blood non-protein nitrogen 36 mg. per 100 cc. The serum carbon dioxide combining power was 45.7 vol. %. The total serum cholesterol was 290 mg., esterified cholesterol 135 mg., and free cholesterol 55 mg. per 100 cc. The blood acetone body level[1] was 6.7 mg. per 100 cc. The Kline and Wassermann tests were positive.

Hypoglycemia was suspected, and the patient was given an intravenous infusion of 1500 cc. of 5% glucose in normal saline solution. He regained consciousness within a few minutes. He was able to take a high carbohydrate diet during the day of admission and thereafter. Because of suspected vitamin deficiency, thiamin, nicotinic acid and Brewer's yeast were also given. On the second morning, the fasting blood sugar level was 90 mg. per 100 cc.

On August 26, 5 days after admission, glucose tolerance test (100 gm. of glucose by mouth) showed the following levels: 109 mg. (fasting), 298, 186, 174, 102 and 95 mg. in ½, 1, 2, 3 and 5 hours respectively. On August 29, an intravenous insulin tolerance test[5] (0.1 units of regular insulin per kilo of body weight) showed the following blood sugar levels: 95 mg. (fasting), 60, 56, 71 and 77 mg. in 20 minutes, 1, 1½ and 2 hours respectively. Adrenalin was then given intramuscularly (0.01 cc. of 1 to 1000 solution). Blood sugar levels of 90 and 91 mg. were obtained 45 and 60 minutes after adrenalin.

On August 22, the total serum protein was 8.2 gm., albumin 5 gm. and globulin 3.2 gm. per 100 cc. On August 28, an intravenous hippuric acid excretion test[7] showed excretion of 0.28 gm. of hippuric acid in 1 hour. This is a subnormal excretion. A Roentgen ray of the skull showed a normal sella turcica, and no other abnormalities. The basal metabolic rate was +1%.

The patient's further course was uneventful, and he was discharged on August 30, 1941.

Comment. The histories of these patients are strikingly similar. In each case a known alcoholic had engaged in a recent bout of drinking. In every case unconsciousness came on 8 to 12 hours after the last known drinking, the patient frequently having slept overnight and awakened before lapsing into hypoglycemic unconsciousness.

Little reliable information could be obtained as to the amount of food recently taken. As with most alcoholics, it might be assumed that they had eaten little.

In the cases of Brown and Harvey, 3 of the 6 patients gave a history of drinking "smoke," a denatured alcohol solvent containing methyl alcohol, gasoline and ethyl acetate. It is well known that an identical preparation sold under the name of "Solox"* is widely

* According to the manual of the United States Industrial Chemical Company, "Solox" is the trade name for a shellac solvent manufactured in accordance with the following formula: Denatured alcohol formula No. 1, 100 gallons; ethyl acetate, 5 gallons; aviation gasoline, 1 gallon. Denatured alcohol formula No. 1 is prepared by adding 5 gallons of methyl alcohol to 100 gallons of 190 proof commercial ethyl alcohol.

used in Richmond as a beverage. It was suspected that all of our patients had been drinking "Solox," but, in spite of considerable effort spent in questioning them, its use could not be established. One of the patients had been drinking bootleg whisky. Another insisted he had drunk only "store whisky." It is likely that the use of "Solox" would be denied because of fear of legal complications.

The physical findings in our cases were similar to those in the Baltimore cases, and were essentially the findings of hypoglycemic coma.[6] All the patients were totally unconscious. In none of our cases was an alcoholic breath odor described. This may be explained by the interval between the last drinking and the onset of hypoglycemic symptoms. The usual neurologic finding was extensor rigidity of all extremities, with increased tendon reflexes. In 1 case, there were fine convulsive twitchings, and in 1, repeated convulsions with opisthotonus. One patient showed flaccid limbs, and no tendon reflexes could be obtained. Conjugate side-to-side movement of the eyes was present in 1 patient. The findings were such that a cerebral accident, particularly subarachnoid hemorrhage, was suspected in most of the cases.

The diagnosis was established by the finding of a very low blood sugar level. In the later cases, glucose was given before the blood sugar levels were reported, and the immediate response established the diagnosis of hypoglycemia. The only other significant laboratory finding on admission was the presence of acetonuria in 3 of the 4 cases, and an elevation of the blood acetone bodies in the 1 case in which this was determined.

In all but 1 of the patients, the response to glucose was immediate, and complete, no relapses occurring. One patient (Case 2) did not recover completely for 2 days. This patient showed other findings that indicated a more fundamental disorder of carbohydrate metabolism, which will be discussed.

Several lines of thought presented themselves when an attempt was made to explain the cause of the hypoglycemia.

First, it was suspected that these patients might have an inherent abnormality of carbohydrate metabolism, hypoglycemia being precipitated by low food intake. The occurrence of repeated attacks in the same individual, both in our cases and in the Baltimore cases, suggested this. Such an abnormality would probably involve an endocrine dyscrasia. The endocrine system was investigated in 3 of the 4 patients. In Case 2, the small stature of the patient, flat glucose tolerance curves, and low basal metabolic rate were definitely suggestive of hypopituitarism. Unfortunately, other studies were not carried out, but it seems very likely that this patient had the "hypoglycemic unresponsiveness" associated with anterior pituitary insufficiency,[5] and that severe hypoglycemia was precipitated by alcoholism and starvation. In the other 2 patients studied, there was no evidence of any endocrine abnormality. The glucose toler-

ance curve was normal in 1, slightly hyperglycemic in 1, and an insulin tolerance test normal in 1. These tests were done after recovery, but should demonstrate any inherent metabolic defect present. Basal metabolic rates were normal, and Roentgen rays of the sella turcica showed no suggestion of pituitary tumor.

The question of liver disease with impaired capacity for glycogen storage was considered. All the patients were chronic alcoholics, and might be expected to have some liver damage. In the 2 patients in whom tests of liver function were done, there was questionable evidence of impaired function in 1. In Case 4 there was diminished excretion of hippuric acid, and the hyperglycemic glucose tolerance curve might be considered as suggestive of liver damage.[4] The serum cholesterol and cholesterol esters were normal, as were the total and fractional proteins. In Case 3 all the liver function tests were normal. Brown and Harvey noted questionable impairment of liver function in 1 of 6 patients. In both groups of cases, most of the studies were done after recovery, and do not indicate the state of liver function on admission. However, it does seem that there is little evidence of any residual liver damage, and that any changes present must have been transient.

In 1 patient, there was a suggestion of vitamin deficiency in the development of symptoms of peripheral neuritis, and thiamin was given. However, we are not aware of any association between deficiency of any of the known vitamins and hypoglycemia. None of the other patients showed any manifestations of deficiency.

Diminished food intake and depletion of liver glycogen may well have been a factor in the development of hypoglycemia in these patients. However, moderate periods of starvation do not lead to severe hypoglycemia.[2] Nor do the great majority of alcoholic patients, many of whom have eaten little, show any such lowering of the blood sugar.

The transient nature of the hypoglycemia and the absence of evidence of endocrine dyscrasia or of liver disease following recovery, suggest that a toxic factor is responsible. It seems likely that these patients had been drinking some form of denatured alcohol, and that one of the denaturing substances present is responsible for the hypoglycemia. Brown and Harvey were unable to demonstrate lowering of the blood sugar in dogs that were fasted for 48 hours, and given "smoke" by stomach tube. Perhaps a longer period of intoxication is necessary to reproduce the picture seen clinically.

The nature of the disturbance of carbohydrate metabolism is not known. We are inclined to agree with the suggestion of Brown and Harvey that there is interference with gluconeogenesis. The blood sugar of a fasting individual is maintained after depletion of the original glycogen stores by the continued release into the blood of carbohydrate formed from protein in the liver.[2] It seems plausible that in these patients, either because of temporary damage to liver

function generally or by specific inhibition of gluconeogenesis by the toxic substance, this conversion is prevented, and hypoglycemia results. The ketonemia and ketonuria observed are probably similar to those seen in other forms of hypoglycemia with or without depletion of liver glycogen,[9] and are thought to be due to excessive breakdown of fat in the liver accompanying increased hepatic glycogenolysis.

Conclusions. 1. Four cases of hypoglycemic coma following alcoholic intoxication are reported.

2. It could not be established what these patients had been drinking.

3. In each case hypoglycemia occurred 8 to 12 hours after the last drinking.

4. The usual clinical manifestations were unconsciousness and extensor rigidity of the limbs with increased tendon reflexes.

5. All the patients recovered when glucose solution was given intravenously.

6. One of the patients was thought to have hypopituitarism. The other patients showed no evidence of any endocrinologic disorder.

7. Following recovery, there was only questionable evidence of impaired liver function in 1 patient.

8. The possible presence in the alcoholic mixture consumed of a substance having a toxic effect on carbohydrate metabolism is discussed.

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DETOXIFICATION OF PROGESTERONE DERIVATIVES IN THE LIVER*

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The liver is the essential organ for the detoxification of estrogens[11,13,16,21,25] and other steroids, especially progesterone.[20] Since pregnanediol is considered the end-product of progesterone metab-

* This investigation was supported by a grant from the John and Mary Markle Foundation.

olism in man,[23] it was thought that this compound might escape detoxification by the liver. This possibility was examined by comparing the activity of pregnanediol in normal and hepatectomized animals. But the results did not necessarily indicate a true detoxification by the liver. Therefore several other possible interpretations of the results were examined such as storage of the steroids in the liver, excretion into the bile, and so on.

Experimental Results. The activity of pregnanediol was compared in two groups of 5 young female rats weighing about 30 gm.; in the first group the animals were hepatectomized by the Selye and Waelsch method, which removes 75% of the liver;[24] the animals in the other group were used as controls. As a test of the activity of pregnanediol, we used the anesthetic power evidenced by this steroid when it is administered by the intraperitoneal route.[19] A single injection of 20 mg. of pregnanediol in 1 cc. of peanut oil was given to rats partially hepatectomized 3 hours previously and to their normal controls. A parallel experiment was performed with pregnanedione, a possible intermediary between pregesterone and pregnanediol. A dose of 5 mg. of pregnanedione in 0.25 cc. of peanut oil was administered intraperitoneally to 5 normal and 5 partially hepatectomized female rats weighing about 50 gm. The results (Table 1) showed a much greater anesthetic activity of the 2 steroids in the partially hepatectomized rats.

TABLE 1.—INFLUENCE OF PARTIAL HEPATECTOMY ON ANESTHETIC ACTIVITY OF PROGESTERONE DERIVATIVES

	Intraperitoneal dose (mg.)	Degree of anesthesia.	
		Intact animals	Partially hepatectomized animals
Progesterone (after Selye)	5	Light	Deep
Pregnanediol	20	None	Light
Pregnanedione	5	Trace	Deep

The reduction in anesthetic activity by the liver may be due to its location in the path of absorption of the steroids since they were intraperitoneally injected. To answer this question, advantage was taken of the fact that, alone among steroids, pregnanedione produces anesthesia even when injected subcutaneously.[19] Five or 10 mg. of this compound were given by the subcutaneous route to normal and partially hepatectomized rats weighing about 50 gm. The difference between the two groups of animals (Table 2) was as marked as in the preceding experiments (Table 1). The anesthesia after removal of the liver lasted over 24 hours and even in one case 51 hours. In the normal controls, there were either no symptoms at all or only a slight excitement in the 2 hours after the injection.

TABLE 2.—INFLUENCE OF PARTIAL HEPATECTOMY ON ACTIVITY OF PREGNANEDIONE GIVEN SUBCUTANEOUSLY

Dose	Degree of anesthesia.	
	Intact animals	Partially hepatectomized animals
5 mg.	None or trace	Deep
10 mg.	Trace	Deep

The possibility that steroids might be stored in the liver without being destroyed was examined by analyzing the extracts from the livers of animals treated with pregnanediol or pregnanedione. Aqueous and ether-alcohol extracts[14] of the liver were tested for the presence of steroids, by intra-

peritoneal injection into partially hepatectomized rats. In the case of pregnanedione, three groups of 4, 7, and 11 rats weighing about 50 gm. received 5 mg. of this compound per animal subcutaneously and were sacrificed at 24, 36 and 48 hours, respectively, after the injection. It must be noted that 24 hours after the injection of the same dose of pregnanedione, hepatectomized rats are in deep anesthesia and their organism is therefore flooded with the steroid. If in the normal animals the steroid were stored in the liver, there would be enough hormone in the liver to induce sleep in a partially hepatectomized rat. However, the pooled extracts of 4, 7 or 11 rats, respectively, did not anesthetize one partially hepatectomized rat. Similar negative results were obtained in one experiment with the livers of 5 rats given pregnanediol.

The possibility that the detoxification was due to the elimination of the steroids in the bile was examined by preventing bile excretion surgically. The two main branches of the bile duct were ligated as closely as possible to the liver in a group of 6 young 50 gm. rats. In addition a third ligature was placed on the main bile duct formed by the junction of the branches. Bile pigments appeared soon in the urine of these animals, indicating interruption of bile secretion by the liver. After checking for the presence of pigment in the urine, a subcutaneous injection of 5 mg. of pregnanedione was given to the animals 24 hours after the operation. In spite of the absence of biliary excretion, no anesthesia was produced, while in intact animals given the same dose of the compound marked narcosis ensued.

Discussion. As long as the increased effectiveness of pregnanediol or pregnanedione after partial hepatectomy was observed only after intraperitoneal administration, it was not an absolute proof of the detoxification of these substances in the liver. It appeared possible that the liver reduced the activity of the steroids only when they were absorbed through the portal vein. When the ability of the liver to inactivate steroids has been observed *in vivo*, it was usually after intraperitoneal administration. Thus Golden and Sevringhaus observed that ovaries transplanted to the mesentery did not induce estrus in spayed females.[8] If later on the same ovaries were placed in the axilla, estrus appeared. Similarly Biskind and Mark found a reduction in the activity of pellets of estrone or testosterone implanted in the spleen, while these pellets were active when placed outside the peritoneal cavity.[2] Evans and Burr with estrone,[5] Segaloff and Nelson with estradiol,[18] Albrieux and colleagues with progesterone,[1*] Fels with estrone and stilbestrol,[6] reported likewise a smaller activity by peritoneal than by subcutaneous administration. It was important to decide whether the liver could also reduce the activity of steroids administered otherwise than intraperitoneally. Subcutaneous administration of pregnanedione to normal and partially hepatectomized animals (Table 2) demonstrated that partial removal of the liver greatly enhanced the activity of the steroid. Therefore the liver decreased the activity of pregnanedione, whatever the path of absorption may be. The quoted experiments[1,2,5,6,8,18] simply indicate that the ability of the

* Recently Fels and Monaco[7] observed no inactivation of progesterone by the liver, contrary to well-established results of Selye[20] and others.[1]

liver to reduce the activity of steroids is more easily exerted in case of absorption through the portal system.

The liver may act on the steroids in three different ways. The compounds are either inactivated by the liver cells (true detoxification), or excreted into the bile, or stored in the liver and released too slowly for their effect to be exerted. Such a storage of the steroids in liver cells, similar to what has been found in the case of cholesterol itself,[17] could explain the reduction in the anesthetic power of the steroid in presence of the liver, since the intrahepatic accumulation of the compound would prevent the flooding of the steroid in the body, necessary for anesthesia.[19] However, the investigations performed with extract of livers showed no anesthetic activity and therefore no accumulation of steroids in that organ.

The possibility of excretion of steroids into the bile was indicated by the finding of estrogens in that fluid.[4,9,10,12] When fairly large amounts of estrogens were injected, only a small percentage of the administered amount, namely 13%[22] or from 1 to 8%[15] could be found in the bile. Such a small biliary excretion could not account for the large increase in the activity of the steroids after removal of the liver. A recent report by Cantarow, A., Rakoff, A. E., Paschkis, K. E., and Hansen, L. P.,[3] indicates that the intravenous injection of very large doses of estrone is followed by a marked excretion of estrogen in the bile. The method of injection and the magnitude of the amounts used are such as to explain the discrepancy between their results and those of other investigators. Indeed our experimental results showed that, in the absence of bile excretion, the liver completely retained its ability to reduce the activity of the steroids.

The only remaining possibility is that of an inactivation, that is to say, a true detoxification of the steroids by the liver tissue. *In vitro* experiments with other steroids led to the same conclusion: thus, estrogens were reported to be destroyed by a liver mash[11,25] or by perfusion through the liver.[13]

Conclusions. 1. Free pregnanediol is detoxified in the liver.

2. Experiments with pregnanediol and pregnanedione indicate that detoxification of these substances by the liver is not essentially dependent upon the path of absorption; it is not due to storage in the liver or to excretion in the bile, but is the result of an inactivation by the liver cells.

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A NEW CONCEPT OF THE CAUSE OF PATENCY OF THE DUCTUS ARTERIOSUS*

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The cause of closure of the ductus arteriosus is a problem which is both fundamental and important to our knowledge of physiology of the fetus at birth and to our understanding of one of the common forms of congenital heart disease, patency of the ductus arteriosus. Yet, this problem has remained unsolved and largely unexplored by experimental research until recently.

There have been many theories put forward to explain the mechanism of closure of the ductus arteriosus, but for the most part these have not been supported by experimentally observed facts. Wells in 1908[3] summarized the more important of these theories of closure as follows: the expansion of the large bronchi at the onset of breathing compresses the ductus arteriosus; thrombosis in its lumen and subsequent adhesion of the walls closes the ductus; bending of the arch of the aorta by increased pressure after birth causes closure; beginning of respiration causes a change in position of the thoracic

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viscera and this causes tension and collapse of the ductus; fibrous growth in the intima leads to occlusion; active contraction of the layers of the wall of the ductus closes it; fibrous bands passing over the ductus are connected with the diaphragm and upon descent of the diaphragm with respiration the bands are pulled down and occlude the ductus; a thin crescentic fold of tissue present at the aortic end of the ductus acts like a valve in preventing the flow of blood from the aorta into the ductus.

Wells had a clear conception of the conditions that must be satisfied for any theory of closure to be valid. He wrote (p. 388) that closure of the ductus "is a physiological process taking place spontaneously and instantaneously in every newborn child, and therefore there must be some mechanism which can be relied upon always to perform this occlusion. Any explanation which involves connective tissue proliferation must be inadequate, for the duct is patent and carrying on its full function up to the moment of delivery, and then is at once occluded when the child begins to breathe; it is necessary to distinguish between the instantaneous occlusion of the duct and its subsequent obliteration."

We have recently presented experimental work which clarifies to some extent the mechanism of closure of the ductus arteriosus (Kennedy and Clark[1,2]), and which forms a basis for a new concept of the cause of patency of the ductus arteriosus.

Using guinea pigs we have found that closure of the ductus normally occurs in two distinct phases: the first is a muscular contraction of the wall of the ductus requiring several minutes, following this the ductus remains closed. The second phase consists essentially in replacement of the muscular tissue in the wall by fibrous connective tissue, resulting in the ligamentum arteriosum. The latter process requires about 1 month in the guinea pig.

Near the end of fetal life the ductus arteriosus is a potentially contractile structure which remains open during fetal life as far as we have observed. However, it has the ability to close in response to various stimuli, to remain closed during continuation of the stimulus, and under certain conditions, to open again after the stimulus has ceased. Under the proper circumstances this sequence of closure and opening can be repeated many times. Mechanical or electrical stimulation of its wall or of nearby tissue will cause it to close promptly within about 1 minute.

Other than mechanical or electrical stimulation, the most reliable stimulus to closure is breathing or intermittent inflation of the lungs with air. In our experiments the onset of normal breathing after birth was always followed by closure of the ductus arteriosus in from 3 to 10 minutes. Inflating the lungs with intermittent puffs of air through a tracheal cannula (in order to simulate breathing artificially) causes closure of the ductus in healthy fetuses within several minutes.

We have also observed closure of the ductus following injection of adrenalin, following mechanical stimulation of the carotid sinus, and after the fetus had experienced a brisk hemorrhage.

It seems likely that under physiologic conditions breathing is the most important cause of closure.

In our artificial breathing experiments (inflation of lungs through a tracheal cannula) we found that when air or pure oxygen is used closure occurs regularly; however, when pure nitrogen is used (oxygen being rigidly excluded from the gas used for inflation), the ductus fails to close. Our observations indicate that oxygen is a necessary component of the inflation mixture for closure to occur. In view of these results, it occurred to us that the introduction of oxygen by a route other than the lungs might cause closure. Without inflating the lungs, oxygen was injected slowly in tiny bubbles into the umbilical vein. This resulted in closure of the ductus.

Our observations have led us to a new concept of the ductus arteriosus. It is a potentially mobile structure and is able to actively close by contraction of its muscular wall in response to certain definite stimuli, much as many other hollow, smooth muscle structures. Under the conditions of our experiments, if the stimulus ceases, the ductus will open again. This active muscular contraction with obliteration of the lumen is the first phase of closure of the ductus arteriosus and occurs during the first few minutes following birth, under normal circumstances, beginning with establishment of effective respiration. In normal animals the ductus remains closed after this initial closure and is finally transformed into the ligamentum arteriosum (Kennedy and Clark[1]).

We believe that it is the interruption of the first phase or the initial closure that causes patency of the ductus arteriosus. In other words it is an interruption of a normally occurring or physiologic process, not some bizarre malformation, which produces this type of congenital heart disease when it occurs unassociated with any other defect.

We have observed patency of the ductus arteriosus, under certain conditions, in guinea pigs which lived several hours after birth.

It is our opinion based upon these experiments, although we are unable to offer direct evidence to support it, that vigorous respiration with high concentrations of oxygen just after birth will promote the prompt closure of the ductus arteriosus in humans.

It seems appropriate here to point out that an approach to this problem through its pathology is inadequate; that is, a study based wholly on postmortem specimens will not give the observer an accurate idea of the true state of the ductus during life. Many times during our experiments we have seen a ductus arteriosus, which was open at the time of the animal's death, close as a result of dissection in the vicinity of the ductus several minutes or longer after death. We have also occasionally observed a ductus arteriosus

which was closed at the time of death, open subsequently, in each instance under abnormal conditions.

We wish to hold up for condemnation the practice of the pathologists in many hospitals of inserting a probe into the ductus arteriosus, especially in the newborn, in order to ascertain whether it is open or closed. Anyone at all familiar with the histologic changes in the ductus following birth realizes that such a procedure is entirely worthless. We are unwilling to accept any data relative to closure of the ductus in which the patency of the ductus was tested in this way.

It should be emphasized that the ductus arteriosus in late fetal life is potentially a mobile or contractile structure and will respond by closure to certain stimuli much the same as many other hollow muscular structures. Therefore, we believe that the problem of closure must be studied by means of a physiologic approach.

Summary. The cause of closure of the ductus arteriosus at birth is important to our knowledge of physiology and of heart disease.

Our observations on guinea pigs show that the ductus is different from the other great arteries both histologically and in its physiologic reactions.

The ductus arteriosus during late fetal life is potentially an active structure and is able to close in response to certain definite stimuli.

It normally closes within the few minutes following birth and remains closed. If this normal process of closure is interrupted, patency of ductus arteriosus results. Thus, it may be the interruption of a normal physiologic process which causes this form of congenital heart disease when it occurs alone, not some bizarre malformation.

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ABNORMALITIES OF THE AMOUNT OF THE CIRCULATION (HYPER- AND HYPOKINEMIA) AND THEIR RELATION TO NEUROCIRCULATORY ASTHENIA AND KINDRED DIAGNOSES*†

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FOR the last 15 years we have been accumulating data on the amount of the circulation of subjects lying at rest, both normal

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persons and patients from the medical wards. At first we employed the ethyl iodide method,[3] in recent years the ballistocardiograph,[4] and about 1600 of these records have been taken. These were filed under appropriate diagnoses and, with the passage of time, certain files have become full enough to warrant detailed analysis of their contents. One of these files contains the records of 68 cases characterized by symptoms referable to the circulation which could not be accounted for by any abnormality demonstrated by the usual hospital procedures; the group usually classified under such vague diagnoses as functional heart disease, neurocirculatory asthenia, autonomic imbalance, sympathicotonia, vagotonia and the like.

By estimating the cardiac output, functional abnormalities of the circulation have been discovered in many of these cases. But, as similar changes have also been found in many patients with organic disease, to enable readers to see the subject of this study in proper perspective it will first be necessary to trace the history of our investigations and to review the state of the circulation found in other clinical conditions.

The first step in the classification of our data was to discover the normal standards for the amount of the circulation,[5] the second was to divide the abnormal cases into two groups: those with circulations above and below normal. This approach has been and still is used to classify and to interpret data concerning blood pressure. When one thus studies the circulation one needs a term to serve the same purpose as the term hypertension, and it was not easy to find a satisfactory word.

One could say that a patient had a "supernormal circulation" or that he suffered from a "supernormal circulatory" state, but such terms seem long and awkward. The term "supercirculation" reminds one unpleasantly of Hollywood; while "hypercirculation," of mixed etomological parentage, derives dignity only by relation to its half-brother "hypertension" whose history certainly shows that a bar sinister is no bar to a place of importance in our language. Turning to the Greek roots "hyperrheaemia," increased flow of blood, proved too difficult to pronounce differently from the familiar "hyperemia." Eventually the term "hyperkinemia," increased motion of blood, was suggested by Dr. J. H. Austin. Easy to say and with a short adjective form, the terms hyperkinemia and hypokinemia have been adopted to indicate the corresponding abnormalities of the amount of the circulation when estimated with the subjects at rest in the supine position.

About 2 years ago our data on the first 100 cases with hypokinemia were published.[6] In Table 1 these data have been reviewed and amplified.

The first two items in this table are based on inferences. Hypokinemia is to be expected in any moribund subject because, in becoming zero at death, the circulation must pass through a hypo-

kinemic stage. There seems to be ample evidence from animal experiments to expect hypokinemia in cases of shock, but this is another inference for we have not worked on shock.

TABLE 1.—OCCURRENCE OF HYPOKINEMIA

Group	Frequency of hypokinemia among all cases in this group
Moribund patients	All
Shock	All ?
In congestive heart failure	Most
Valvular heart disease not in failure	About 1/2
Coronary heart disease:	
Chronic angina pectoris	Almost all
Soon after infarction	About 1/2
Hypertension	About 1/3
Endocrine diseases:	
Myxedema	All
Pituitary or adrenal	Many
Convalescence from severe febrile disease	About 3/4
Essential hypokinemia	26 cases

Our data show that hypokinemia is to be found in most, but by no means all, cases of congestive heart failure. Of the cases of valvular heart disease not in failure the abnormality is encountered frequently, chiefly in those who have been in failure or who are in danger of it. In chronic angina pectoris hypokinemia is the rule and its presence often provides welcome objective evidence of the presence of this condition. Over one-third of the cases of hypertension show hypokinemia, chiefly those with small hearts. Severe cases of certain endocrine diseases usually have it. It is very common in convalescence from the severe acute infections. Finally in our data are 26 cases in which hypokinemia was found without any disease to which it could be attributed, and these cases fall into the group which is the subject of this study.

It took almost 3 years longer to assemble 100 cases with hyperkinemia and our first publication on this subject is now in press.[7] The results pertinent to this discussion have been summarized in Table 2.

TABLE 2.—OCCURRENCE OF HYPERKINEMIA

Group	Frequency of hyperkinemia among all cases in the group
Healthy persons	A very few
Hyperthyroidism without cardiac complications	Almost all
Extreme emaciation	About 3/4
Patent ductus arteriosis	Most
Peripheral A–V aneurisms	Few
Anemia	About 1/4
Febrile disease tested late in the course	A few only
Hypertension	A very few
Pulmonary:	
After pneumonectomy	4 of 5 cases
In chronic disease	A few
Essential hyperkinemia	20 cases

In analyzing the hyperkinemic group there is a difficulty which is absent when hypokinemia is studied. Excitement may cause

hyperkinemia in anyone, therefore an isolated instance is of no importance. The occurrence of 16 instances of the abnormality in tests of over 400 healthy persons can be accounted for partly by excitement in class demonstrations, partly by chance cumulation of inherent errors; for, working with methods containing errors which we believe to be large, one has no right to expect a perfect division between normal and abnormal. In the healthy group, whenever the test was repeated, the second value was normal, a fact which distinguishes this group from those to follow.

Almost all cases of hyperthyroidism without obvious cardiac involvement show hyperkinemia, as is well known.

The hyperkinemia of emaciated persons is partly a matter of definition, for their circulations were above normal in relation to their present body weight, not to what they should have weighed.

Most of our cases of patent ductus arteriosis had hyperkinemia, as has been found by others; but only one of 4 cases of traumatic peripheral arteriovenous communications showed this abnormality. Doubtless it is a matter of the size of the communication.

In cases of anemia with hemoglobin under 60%, hyperkinemia was found less frequently than the literature had led us to expect. This was also the case in the febrile diseases. Stimulation of the circulation during the fever following the administration of pyrogens is easily demonstrated, but only 1 of 8 cases tested during the later half of a febrile disease showed hyperkinemia.

The few cases with hypertension who also had hyperkinemia formed a consistent group. All were extremely ill and all but one had marked cardiac hypertrophy.

We were surprised to find hyperkinemia in 4 of 5 cases after surgical removal of one lung, and we have encountered it rarely in chronic pulmonary disease. Hyperkinemia was also found in 7 cases with nothing in common which we could discover and, as excitement may cause this abnormality in anyone, such isolated instances deserve no attention.

Finally, in our data are 20 cases in which no reason for the abnormality was discovered, and these cases fall into the group which is the subject of this study.

Let us stop to compare these cases of essential hyperkinemia with the corresponding hypokinemic group. Figure 1 shows that the distinction is not difficult when their ballistocardiograms are available. The symptoms of these 2 patients were rather similar; I have little doubt that most of us would have been content to classify them under the same heading. But the difference in the impacts of their circulations was so very great that the physiologic mechanisms at fault must certainly have been very different.

A comparison of the clinical pictures of the two groups is given in Table 3. Both consist chiefly of young adults who think of themselves as nervous, but then the similarity becomes less marked.

The hypOS are weak and dizzy; they complain of dyspnea on exertion, and about one-fourth of them are subject to repeated fainting attacks. The hypERS deny weakness, dizziness is a minor factor, and there is no fainting among them. Indeed they do not usually

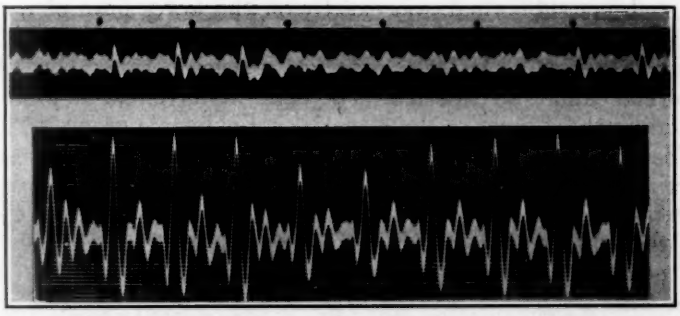

FIG. 1.—Ballistocardiograms from a hypokinemic patient (top) and a hyperkinemic patient (bottom). The time, in seconds, is indicated over the top record. Both records were taken with the subject horizontal after 15 minutes' rest. Reproductions one-half actual size.

Top.—E. G., a woman aged 46, wt. 151, B.P. 140/90, CC (chief complaint): Repeated fainting attacks. P.E. negative: orthodiagram, heart normal size; EKG normal. Cardiac output −30%.

Bottom.—J. D., a man aged 25, wt. 147 pounds, B.P. 150/70. CC: Spells of faintness not confined to upright position. P.E. negative. B.M.R. +13. Cardiac output +57%.

think of themselves as ill, although they are underweight and tend to have rapid heart rates. An experienced clinician, inspecting cases of essential hypokinemia, gets no very definite impression about the diagnosis, but the patients with essential hyperkinemia are immediately suspected of having hyperthyroidism and only after repeated estimations of basal metabolic rate is this diagnosis abandoned.

TABLE 3.—SYMPTOMS IN ESSENTIAL HYPO- AND HYPERKINEMIA

	HypO	HypER
Average age, years	36	32
Deviation from ideal weight, pounds	+6	−13
Average pulse rate	74	90
Symptoms—Nervous	++	++
Weak	+++	0
Dizzy	+++	+
Fainting	+	0
Dyspnea on exertion	+++	+
Average B.M.R., %	−8	−3
First impression	?	Hyperthyroidism

The two groups which we have called essential hyper- and hypokinemia, characterized by these abnormalities of the resting circulations, without any known pathologic change to account for them, comprise two-thirds of the group which is the subject of this study, or 46 out of a total of 68 cases. The remaining 22 cases, without

any abnormality of the circulation detected at rest, must now be considered.

Seven of these cases exhibited the symptoms of weakness and dizziness, and the proneness to fainting attacks characteristic of the essential hypokinemic group. In these the resting circulation, although not subnormal, was exactly on the lower limit of normal. Since our estimates of the amount of the circulation include errors which we believe to be large, a perfect division between normal and abnormal cannot be expected. Therefore we have had no hesitation in adding these cases to the essential hypokinemic group.

The remaining 15 cases have less in common. Seven were characterized by having all their symptoms in attacks, they considered themselves well and free of symptoms between these episodes. But the attacks were of various characters; spells of weakness and faintness, and attacks of palpitation were most common. All these cases were diagnosed neuroses and in some the neurotic origin of the symptoms seemed obvious. Thus a coal miner, subject to attacks of shortness of breath without obvious cause, gave the history that his best friend had recently been invalided by silicosis.

Four of these 15 cases gave lifelong histories of neurotic manifestations; 2 were chronic neurasthenics, one had a history of over 30 admissions to the hospital.

In the 4 remaining cases, although their circulations were normal when they lay at rest, we were able to demonstrate a circulatory abnormality of another type by means of a test which has been studied only recently and therefore was not applied to the great majority of the cases in this series.

If a healthy person, after lying down for 15 minutes, arises and stands still, the circulation diminishes for approximately the first minute of standing and then remains constant for 10 minutes or longer. Therefore to compare the lying and standing circulations of our subjects we took records after 15 minutes rest horizontal, and 2½ minutes after arising. In most subjects tested the impacts of each heart beat diminished after arising but the heart rate increased. When the circulation per minute was calculated these changes tended to cancel each other, the ratio of the lying to the standing circulation averaging 1 to 1 in 50 healthy persons.

Figure 2 illustrates ballistic records obtained both lying and standing in 1 healthy person and 3 of our patients. Evidently some of our patients were unable to make this adaptation properly; when they arose, not only the rate but also the output per beat was much increased, so that the relation of their circulation in the two positions was profoundly abnormal. It was while the cardiac output was abnormally elevated that these subjects had symptoms such as dizziness and faintness, a finding contrary both to my expectations and to the viewpoint generally taught. Apparently these patients suffer from an incoördination of the circula-

tion, a failure to adapt it to the needs of the situation in a normal manner. I am hopeful that such demonstrations will aid in explaining the symptoms of some of the cases in which nothing abnormal is disclosed by either the ordinary clinical examination, or an estimation of the resting circulation.

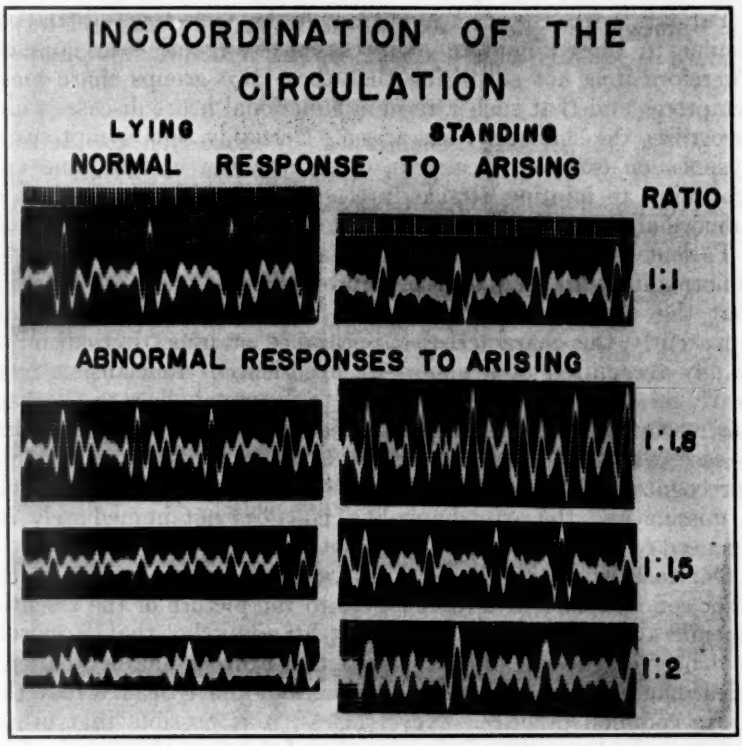

FIG. 2.—Ballistocardiograms after 15 minutes' rest horizontal and about 2 minutes after arising. The time record on the top applies to all the records, largest interval is equal to 1 second. The reproductions are one-half actual size.

Top row. M. T., a normal young woman aged 25, 5 feet 4½ inches, 140 pounds, B.P. lying 135/85, standing 135/90. Cardiac output both lying and standing does not deviate from the normal average.

Second row. F. W., a man of 36, 5 feet 9½ inches, 126 pounds, B.P. lying 114/88, standing 122/98. Studies all negative. CC: Dizziness on arising, fear of falling when upright. Cardiac output +13% lying, +100% standing.

Third row. P. M., a woman aged 42, 5 feet 3 inches, 128 pounds, B.P. 130/90 lying, 120/100 standing. All studies negative. CC: Palpitation, dyspnea on exertion, choking attacks at night. Cardiac output lying −17%, standing +22%.

Fourth row. P. C., a man aged 56, 5 feet 10 inches, 113 pounds, B.P. lying 112/68, standing 107/78. P.E. negative except that patient is very thin. CC: Fainting attacks especially in summer. Cardiac output lying −22% when referred to his actual weight, but −30% if referred to what he should weigh. C.C. standing +56% referred to actual weight.

We can conclude, therefore, that the great group of patients with symptoms referable to their circulations, but without disease

demonstrated by the usual clinical tests, can be properly divided into three sub-groups depending on the condition of their resting circulations. In the hyper- and hypokinemic groups, and in a few patients of the normokinemic group, we have demonstrated an abnormality of function which may well be the cause of many of their characteristic symptoms.

Patients with essential hypokinemia have resting circulations similar to those found in many cases of organic heart disease. Therefore it is not surprising that these two groups share many symptoms and that such a term as functional heart disease, which recognizes the similarity, has arisen. Certainly such symptoms as dyspnea on exertion, weakness, dizziness when upright, and susceptibility to fainting attacks, are consistent with the findings of subnormal circulation.

Patients with essential hyperkinemia share their circulatory abnormality with cases of hyperthyroidism, and it is not surprising that they have much the same appearance to gross inspection. Apparently the characteristic appearance of hyperthyroidism, so readily recognized at a glance by experienced clinicians, is more nearly related to the circulation than to the metabolic rate. Perhaps this is why patients with hyperthyroidism complicated by a cardiac disease which has reduced their circulation, may pass so long unrecognized. Without hyperkinemia the characteristic appearance is missing and the attending physician does not immediately see the need of an estimation of basal metabolic rate.

Our task would not be complete without an attempt to fit the older conceptions and terminology into the picture of the essential kinemic abnormalities. I must start by admitting that I, myself, have been diagnosing all these cases either neurocirculatory asthenia or cardiac neurosis without discrimination, and I believe that this is the common practice. Nevertheless, it is possible that others may have had more discrimination than I, for the older terminology may be fitted into the newer conceptions.

My cases with hyperkinemia seem entirely similar to the soldiers in the last war described by Peabody, Wearn, and Tompkins,[2] who called the condition "irritable heart;" and many readers will recall the controversy with Harlow Brooks as to whether they were really cases of hyperthyroidism. In civil life similar cases have been described by Kessel and Hyman[1] under the name "autonomic imbalance," and in Europe under such names as "parabasadowism" and "sympathicotonia." For cases with hypokinemia the term "neurocirculatory asthenia" is quite descriptive, and I suspect that the term "vagotonia" has also been used to characterize such patients. The term "cardiac neurosis" might be reserved for the normokinemic group. But such an attempt to unite the new and old conceptions would lead to great confusion in the minds of many who have fixed ideas as to what such terms mean.

There is a great deal to be said for a purely functional classification based on the most fundamental physiologic abnormality yet demonstrated. Therefore I propose to subdivide the patients with symptoms referable to their circulation, but without heart disease, into hypo-, hyper- and normokinemic groups, until better knowledge can provide an etiologic classification.

As in the case of hypertension, it is the ability to measure the abnormality which permits an investigation of its etiology to begin.

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THE EFFECT OF FOOD AND ALKALI ON THE ABSORPTION AND EXCRETION OF SULFONAMIDE DRUGS AFTER ORAL AND DUODENAL ADMINISTRATION

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A number of factors are known to alter the absorption of sulfonamide drugs from the gastro-intestinal tract, both in experimental animals and in man. Administration in the form of the sodium salts,[3,11,13,17] or the simultaneous administration of sodium bicarbonate or magnesium oxide[1] increases the absorption of some of the commonly used sulfonamides. It has also been shown that sodium sulfapyridine is absorbed more rapidly and more completely in a subject with achlorhydria than when hydrochloric acid is present.[11] Conjugation with certain substances, including glucose,[15] guanidine,[7] succinylic acid[10] or acetic acid[4,13] produces compounds which are poorly absorbed when given orally. This decreased

absorption is not related to solubility since the resulting compounds, except in the case of the acetyl derivative, are much more soluble than the parent drugs. Marked and unexplained individual differences in absorption of sulfonamide drugs have been noted frequently, both during actual therapy of patients with infections and in the course of studies in normal subjects.

It is known that sulfanilamide differs somewhat from its common derivatives with respect to absorption and excretion. Most striking is the comparatively good absorption of sulfanilamide from the rectum, whereas very little sulfapyridine, sulfathiazole or sulfadiazine is absorbed from this site.[9,13,16,17] Stead and Kunkel[12] found that the maximum blood concentration of sulfanilamide occurred in 10 to 13 minutes after a 1% solution was put directly into the duodenum. It has also been shown that sulfapyridine delays the emptying time of the stomach in human subjects.[8]

In this paper are presented the results of studies on absorption and excretion of a single dose of several sulfonamide drugs in normal human subjects after oral and after duodenal administration. The effects of a meal, of the simultaneous administration of sodium bicarbonate and of administration in the form of the sodium salt were also studied.

Materials and Methods. The subjects were healthy ambulatory males from 16 to 60 years old. A 5 gm. dose was given in all experiments. Tap water (500 ml.) was given with the drug and approximately 150 ml. of fluids per hour was given throughout the first day. All the urine passed during the first 72 hours was collected and the amount of drug excreted in this period was used as an index of the amount absorbed. The drugs were given as powdered suspensions or as solutions in water. Drug levels in blood were determined at appropriate intervals by the method of Bratton and Marshall.[2] In the studies on "fasting" subjects, all food was withheld from the time of the evening meal (about 5 P.M.) until the drug was given, between 8 and 9 A.M. the next day, and breakfast was given from 1 to 2 hours after the drug. Sodium bicarbonate, when used, was given with the sulfonamide in 5 gm. amounts. Duodenal administration was accomplished through a Rehfuss' tube, the position of which was verified fluoroscopically. Several experiments were done in each subject, although not all the different experiments were carried out in any given subject. Two or more days were permitted to elapse after the urine was completely free of sulfonamide drugs before starting another experiment.

Studies with Sulfanilamide (See Table 1). When a single 5 gm. dose of sulfanilamide was given before breakfast, absorption was very rapid. The maximum blood concentration was high and was obtained at the time when the first sample was drawn, namely after ½ hour. About 75% of the administered drug was recovered from the urine in 72 hours. Similar results were obtained when this drug was given directly into the duodenum. When the same amount of drug was given after breakfast, absorption was delayed, the maximum blood level was lower and the amount of drug recov-

ered in the urine in 72 hours was slightly greater. A 5 gm. dose of sodium bicarbonate given with the drug after a meal had no effect.

TABLE 1.—MAXIMUM BLOOD LEVELS AND URINARY EXCRETION AFTER A SINGLE 5-GM DOSE OF SULFANILAMIDE

Mode of administration.	No. of subjects.	Maximum blood concentration.		% of administered dose recovered in urine in 72 hours.*
		Mg. per 100 ml. (total*).	Hours after administration.	
Oral; before breakfast	3	10	½	76
Oral; after breakfast	2	8.1	3	82
Oral + $NaHCO_3$; after breakfast	1	7.8	3	80
Duodenal; before breakfast	2	10.2	½	76

* Mean values.

A Comparison of Oral and Duodenal Administration of Sulfapyridine, Sulfathiazole and Sulfadiazine. These 3 drugs were handled quite differently than sulfanilamide when given directly into the duodenum. This is seen from the data summarized in Table 2. Absorption was much more rapid after duodenal as compared with oral administration. The maximum blood concentrations of these drugs when given by duodenum were reached early, namely in 1 hour in the case of sulfathiazole and in 3 hours in the case of sulfapyridine and sulfadiazine. The maximum levels, however, were considerably lower than when the corresponding drugs were given by mouth. Furthermore, the amount of drug recovered in the urine in the first 72 hours after the duodenal administration was only about one-half of the amount that was recovered when the same amount of drug was given by mouth.

TABLE 2.—ORAL VERSUS DUODENAL ADMINISTRATION OF A SINGLE 5-GM. DOSE OF SULFAPYRIDINE, SULFATHIAZOLE AND SULFADIAZINE

Drug.	Route.*	No. of subjects.	Maximum blood concentration.		% of administered dose recovered in urine in 72 hours.†
			Mg. per 100 ml. (total†).	Hours after administration.	
Sulfapyridine	Oral	2	7.7	6	70
	Duodenal	2	2.2	3	42
Sulfathiazole	Oral	3	6.7	3	68
	Duodenal	3	2.8	1	34
Sulfadiazine	Oral	4	5.5	7	54
	Duodenal	6	3.2	3	30

* All doses given before breakfast.
† Mean values.

Further attempts were made to influence the absorption after duodenal administration. The simultaneous administration of the patient's own fasting gastric juice, or of 80 ml. of N/10 hydrochloric acid or of an equal amount of sodium bicarbonate were tried in individual subjects, but none of these procedures had any effect on the maximum blood levels or on the amount of drug recovered from the urine. When the dose was divided and given in 4 equal

parts over a period of 1½ hours, there was a slight increase in the amount recovered in the urine, as was shown to be the case with sulfaguanidine given orally in this manner.[7]

The Effect of Alkali and of Administration After a Meal on the Absorption and Excretion of Sulfadiazine. The remaining studies were carried out with sulfadiazine and sodium sulfadiazine and are summarized in Table 3. The highest and lowest values obtained in different subjects are noted and give some idea of the individual variations observed. The mean values of the blood levels and of the cumulative urinary excretions obtained at different times following the administration of a 5 gm. dose of sulfadiazine given in different ways are shown graphically in Figure 1.

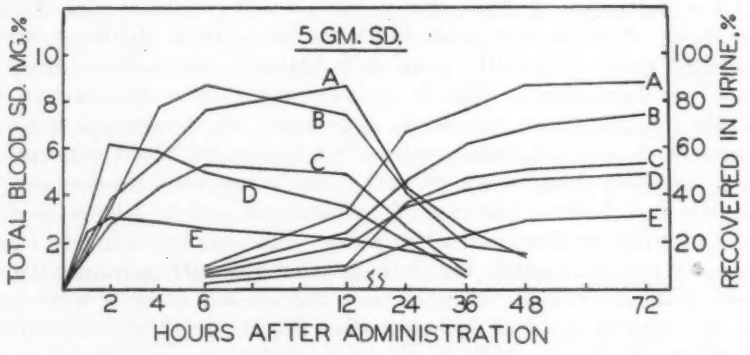

FIG. 1.—"Total" sulfadiazine blood concentrations and cumulative urinary recoveries after administration of a single 5-gm. dose of sulfadiazine in human subjects (mean values). *A*, Oral + $NaHCO_3$; after breakfast. *B*, Oral; after breakfast. *C*, Oral; before breakfast. *D*, Oral + $NaHCO_3$; before breakfast. *E*, Duodenal.

When sulfadiazine was given by mouth before a meal it was absorbed much better than after instillation into the duodenum. The maximum blood levels, although attained later, were almost twice as high after oral as after duodenal administration, and the amount of drug recovered from the urine in 72 hours was almost twice as great. The addition of an equal amount of sodium bicarbonate to the sulfadiazine given by mouth to the fasting subjects resulted in a decided acceleration of the absorption. The maximum blood levels were appreciably higher and were attained much sooner than when the drug was given alone. The amounts recovered in the urine in 72 hours, however, were about the same regardless of whether or not the alkali was given. Similar results were obtained with sulfathiazole by Barlow and Climenko.[1]

When the dose of sulfadiazine was given after the morning meal, absorption was consistently more complete. The maximum blood levels were higher than in the subjects who received the drug before

a meal, even with bicarbonate of soda, and on the average about 25% more of the drug was recovered from the urine. The administration of sodium bicarbonate with the dose of sulfadiazine given after a meal seemed to have a delaying effect on absorption of the drug in the 2 subjects studied.* The maximum levels were about the same but they were attained somewhat later, and the total amount recovered from the urine was appreciably greater, averaging 92% of the administered dose.

Results with Sodium Sulfadiazine. In general, the sodium salts of sulfapyridine, sulfathiazole and sulfadiazine are absorbed more rapidly than their respective free acids when administered orally.[3,11,13,17] The results of the present studies with sodium sulfadiazine are summarized in the lower part of Table 3.

TABLE 3.—MAXIMUM BLOOD CONCENTRATIONS AND URINARY EXCRETION OF A SINGLE 5-GM. DOSE OF SULFADIAZINE: EFFECT OF ADMINISTRATION WITH ALKALI OR AFTER A MEAL

Mode of administration	No. of subjects	Maximum blood concentration. Mg. per 100 ml. (total)			Hours after administration			% of administered dose recovered in urine in 72 hours.		
		High	Low	Mean	High	Low	Mean	High	Low	Mean
Duodenal; before breakfast	6	3.8	2.1	3.2	6	2	3	32	26	30
Oral; before breakfast	4	6.6	3.9	5.5	12	4	7	70	30	54
Oral + $NaHCO_3$; before breakfast	3	8.4	5.5	6.9	3*	2	2	84	24	48
Oral; after breakfast	5	9.6	7.3	8.7	6	4*	6	86	61	77
Oral + $NaHCO_3$; after breakfast	2	9.0	8.2	8.6	12	12	12	96	85	92
Sodium sulfadiazine.										
Duodenal; before breakfast	1	..	..	17.6	..	..	½	..	..	86
Oral; before breakfast	3	16.0	15.2	15.5	1½*	½	½	86	74	80
Oral; after breakfast	3	15.0	6.8	10.2	3	3	3	78	60	67

* This result was obtained in only 1 of the subjects.

When sodium sulfadiazine was given before breakfast, either orally or into the duodenum, absorption was very rapid. The maximum blood level was usually attained within ½ hour, the time when the first blood sample was drawn. The blood concentrations at this time were all more than 15 mg. per 100 ml. This is comparable to the levels observed shortly after intravenous administration of the same dose.[9] If due allowance is made for the sodium content of the administered drug, the urinary recoveries were also similar to those obtained following intravenous administration. When the sodium sulfadizaine was given after breakfast, the results were somewhat similar to those noted with sulfanilamide. Absorption was delayed, but in this instance it was less complete. The maximum blood levels were lower and were attained later, and an appreciably smaller amount of drug was recovered from the urine.

* It is to be noted that no blood samples were obtained between 6 and 12 hours, so that the maximum levels probably occurred within this period and probably were higher than the maximum observed.

Individual variations were greater when the dose followed the meal than when it was given before breakfast.

The subjects used in this study had free hydrochloric acid in their fasting stomach. The pH of the 1% sodium sulfadiazine solutions used was between 9 and 9.5. Three experiments were done *in vitro* with such solutions to determine the effect of adding dilute hydrochloric acid. It was found that most of the drug was precipitated out of solution between pH 7.5 and 8.0. More than 90% of the dissolved drug was precipitated, presumably as the free acid, at pH 7.5. Although gastric juice containing free hydrochloric acid has been shown to have some buffering effect,[11] it is very likely that the pH of the gastric contents in the present experiments was lower than 7.5 and that, for the most part, the free acid was precipitated out from the administered sodium salt in the stomach.

Observations on Abnormal Subjects. There was an opportunity to study the absorption of a single oral dose of sulfadiazine in a patient with non-tropical sprue. The blood levels attained were low and only 20% of the administered drug was recovered from the urine. A vitamin A absorption test done at the same time showed that this substance was likewise poorly absorbed. In a patient with pernicious anemia, sulfadiazine given orally before breakfast was found to be well absorbed. The maximum blood level was 9.6 mg. per 100 ml., 6 hours after administration of 5 gm., and 87% of the dose was recovered from the urine.

Discussion. Perhaps the most interesting fact brought out in these studies is the poor absorption of sulfapyridine, sulfathiazole and sulfadiazine after duodenal administration, as compared with the absorption of the same drugs when given orally. This is in marked contrast to the rapid and almost complete absorption after duodenal administration of sulfanilamide and sodium sulfadiazine, and probably also of the sodium salts of sulfathiazole and sulfapyridine, although these were not studied. It is only reasonable to assume that the portion of the sulfapyridine, sulfathiazole and sulfadiazine not excreted in the urine is largely found unchanged in the large bowel. From there, these drugs are poorly absorbed,[9,13,17] and eventually are eliminated in the stools. It is suggested, therefore, that where large bowel bacteriostasis is desired it may be more advantageous to give such highly effective drugs as sulfathiazole or sulfadiazine directly into the duodenum, in preference to the less effective sulfaguanidine by mouth. The concentration of the former drugs in the feces after oral administration has been found to be low.[5]

The effect of giving a dose of drug after a meal was to delay absorption in every instance. With respect to the total amount absorbed, as reflected in the amount recovered in the urine, the effect of taking a meal shortly before the drug varied with the com-

pound used. With sulfanilamide there appeared to be little or no effect; with sulfadiazine the total amount recovered in the urine was appreciably greater and with sodium sulfadiazine the urinary recovery was slightly less (after allowing for the sodium content of the administered drug) than when the dose was taken on a fasting stomach. The explanation of these differences is not apparent.

The effect of food and of alkali on the absorption and excretion would seem to explain at least some of the discrepancies noted in clinical and experimental studies. It is likely that the kind of food ingested has a decided influence both on absorption and conjugation of sulfonamides, as indicated in some recent reports,[6,14] but this aspect was not investigated.

The amounts present as "free" and as "total" drug were determined on every sample. All of the values mentioned in the text represent "total" drug values. The amount of drug excreted in the conjugated form in different experiments varied from 17 to 25% of the total at 12 hours and from 22 to 35% of the total in 72 hours. The differences in the amount of conjugation observed following various modes of administration were too inconstant to permit any deductions.

Summary and Conclusions. 1. Sulfanilamide is absorbed very rapidly and completely when it is given orally or into the duodenum. Food delays absorption of the drug but does not diminish the amount excreted in the urine.

2. Sulfapyridine, sulfathiazole and sulfadiazine are poorly absorbed from the duodenum.

3. Sulfadiazine is absorbed more slowly but more completely when it is given after a meal than if it is given on a fasting stomach. Alkali appears to increase the amount of drug absorbed when it is given with sulfadiazine after a meal. Sodium bicarbonate hastens the absorption of sulfadiazine when given on an empty stomach, but does not increase the amount absorbed.

4. Sodium sulfadiazine is rapidly absorbed from the duodenum or after oral administration in a fasting subject. Absorption is delayed and is less complete if it is given after a meal.

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BOOK REVIEWS AND NOTICES

THE MODERN ATTACK ON TUBERCULOSIS. By HENRY D. CHADWICK, M.D., Medical Director of Middlesex Tuberculosis Sanatorium; Formerly Commissioner of Public Health of the Commonwealth of Massachusetts, and ALTON S. POPE, M.D., Deputy Commissioner of Public Health and Director of the Division of Tuberculosis, Commonwealth of Massachusetts. Pp. 95; 5 figures and 8 tables. New York: Commonwealth Fund, 1942. Price, $1.00.

THIS is an excellent review of the principles and to some extent the practices that have played a part in reducing tuberculosis morbidity and mortality in the United States. The book will be of value chiefly to public health officers and administrators. It contains chapters on the epidemiologic aspects of tuberculosis, diagnostic procedures, case finding, and the rôle of the sanatorium in control and treatment. The final chapter deals with various phases of an adequate community campaign for the eradication of tuberculosis. Naturally, in a book of this length it is not possible to discuss in detail methods of diagnosis and treatment of tuberculosis.

H. H.

ACUTE INJURIES OF THE HEAD. By G. F. ROWBOTHAM, B.Sc. (MANCH.), F.R.C.S. (ENG.). Pp. 288; 124 illustrations. Baltimore: Williams & Wilkins Company, 1942. Price, $6.00.

THE publication of this book is timely, for all members of the medical profession whether or not in military service should have an authoritative source for consultation upon the proper treatment of cranial injuries. The author has had experience with air-raid casualties and hence brings to his readers the problems inherent in the treatment of this rather special type of casualty. After a discussion of the mechanism of injuries of the head in which, in discussing fractures, the point is made that it is not the injury to the bone but to the brain that is important, the various types of closed cerebral lesions are described together with their underlying pathology. Concussion and compression are the commonest causes for a fatality, and death occurs usually within the first 24 hours following injury. Contusions, lacerations and hemorrhage are the 3 primary lesions of the brain following injury, all due in these closed lesions to abrupt movement of the brain within the skull. The diagnosis and treatment of such injuries are thoroughly discussed and the Reviewer was pleased to note that the suggestion was forcefully made that, when in doubt as to the position or type of the lesion, prompt recourse be had to exploratory trephines or air injection. Chapter IV is especially valuable, for it describes in detail and lays stress upon the pre- and postoperative care of such cases, together with an outline of the proper surgical technique. In Chapter V the methods of handling open or compound wounds are described, together with considerable advice about the treatment of air-raid casualties. The illustrations in the chapter on the technique used in the management of compound fractures are valuable. The final chapters are devoted to the results of injury to special parts of the brain and to the sequels to injuries of the head.

This is a worthwhile book which presents a difficult subject with very little lost motion. The type is clear and easy to read. The illustrations, as has been noted, are numerous and on the whole excellent. Both the author and publisher are to be congratulated.

F. G.

SOLVING SCHOOL HEALTH PROBLEMS. The Astoria Demonstration Study. By DOROTHY B. NYSWANDER, PH.D., Director of the Study. Pp. 377; several tables. New York: The Commonwealth Fund, 1942. Price, $2.00.

PUBLIC school health programs have aroused dissatisfaction in recent years since the technique—medical and educational—of conducting health examinations has developed rapidly but the organization methods of supplying these to the public still rest in the Middle Ages. This report of Dr. Nyswander is really the culmination of a progressive series which started first with a survey of school health in about 90 cities of varying sizes, then a study of a sample of school children and their health and finally a survey of the methods used in detecting and correcting physical defects in New York City schools. The report then sets forth the applications of modern administrative methods to the great health problem in the public schools of a representative section of our largest city.

The study was sponsored by a variety of organizations such as the American Child Health Association, the Milbank Fund and the Metropolitan Life Insurance Company, etc., and carried out by a field staff with an advisory committee of physicians and public health experts. How to bring Public Health in all respects including its educational aid to a quarter of a million children, and indirectly to their parents, was the core of the problem—these children and parents springing from varying backgrounds of race, religion, intelligence, language and superstitions. How to develop up-to-date administrative and field methods of public health in schools in, around and through an inadequate system without disrupting too much the functioning program was the active problem. How skillfully, practically and how adequately this was done the reader can judge only by careful perusal of this report. An old method of screening out sick, undernourished and handicapped children was gradually eliminated and another coördinated and more practical substituted. Simplified record and "follow-up" systems were devised. Coöperation between teachers, parents, school physicians and private physicians was secured to the mutual advantage of all, and especially the children.

The book begins with a description of the school health program used in New York City in 1936 and a survey of the district selected for the study. Then there is a description of the school physician and his job, the usual findings of the school health examination, and follow-up of cases, the work of the teachers in a first-class program, the duties of the school nurse and finally a discussion of records and their availability.

Problems of visual testing, hearing, dental care, and the direction and management of children with cardiac diseases were skillfully posed and solved. The final stage of the study was devoted to the education of others in the methods, techniques and point of view developed during the earlier years of the Astoria District Study. Thus the whole city reaped the benefit of a localized demonstration in school health. The results: a more thorough physical examination of more children, elimination of long delays in securing correction of defects, avoidance of conflicts of professional opinion, increased interest in health problems of school children by officials and others in the city and finally the development of an up-to-date school health staff in New York City.

The aim of a school health service is not only the detection and correction of defects but also the development of a real concern for *positive* health and its relation to education. This demonstration has led the way in our country in public school health administration. Other valued items of interest in the volume are the descriptive charts of the record cases used, the classification of cardiac cases, and the exhibits, which are in the appendix.

E. T.

A SHORT HISTORY OF NAUTICAL MEDICINE. By LOUIS H. RODDIS, M.D., Captain, Medical Corps, United States Navy. Pp. 359; 12 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $3.00.

THOUGH secondary sources for nautical (maritime) medical history may be copious, as is indicated in a final bibliographic note in this volume, there seems to be no one place where even the high spots of the subject have been adequately collected in one volume. One, therefore, welcomes all the more this compact history, which includes the results of the author's studies of U. S. Naval Medicine. It is good to know also that his biographies of the Surgeon Generals of the U. S. Navy are already appearing in the *U. S. Navy Bulletin*.

The chapters cover nautical medicine of classical and medieval times, the diseases characteristic of the old sailing ships, naval medical departments, hygiene, hospitals, uniforms, the medicine of the merchant marine and nautical research.

Greek and Roman practices, James Lind and Scurvy, "Yellow Jack," Gilbert Beane and Thomas Trotter are among the topics considered. The chapter on U. S. Naval Medicine, which occupies a good quarter of the volume, selects Lewis Heerman, of Tripoli fame; Edward Cutbush, "The Nestor of the Medical Corps of the Navy" and author of the first American work on Naval Medicine; and W. P. C. Barton, First Chief of the Bureau of Medicine and Surgery for special notice. On page 250 are given the 10 chief contributions of the Medical Department of the U. S. N. to nautical medicine and on pages 351–4 a useful table of important chronologic events in naval medicine.

We welcome a book on this subject, especially at the present time and especially when it is as well and entertainingly done as is this volume by Captain Roddis. E. K.

LEUKÆMIA IN ANIMALS. By JULIUS ENGELBRETH-HOLM, M.D., Director of the Cancer Research Laboratory of the Danish Anti-Cancer League; Chief Pathologist of the Finsen Institute and Radium Station of Copenhagen. Pp. 245; 44 figures. Edinburgh: Oliver & Boyd, 1942. Price, 15/-n.

THIS well-written book might serve as a text to illustrate the multiplicity of methods used and their coördination by modern students of disease. The author points out that it was in 1858, 12 years after the recognition of human leukemia by Virchow, that Leisering reported the first case of leukemia in an animal—the horse. The first transmission experiments were attempted in 1872, but were unsuccessful until 1908, when Ellermann and Bang transmitted leukemia from diseased to healthy fowls.

The spontaneous leukemias in birds and mammals are treated separately, then their experimental production as well as numerous transmission experiments are considered. The hereditary factors, which have been so successfully investigated by Americans, are dealt with in detail. The author believes that leukemia is a neoplasm, and what he says of its occurrence in fowls might well serve as a general conclusion: "In spite of much consideration, in spite of the study of a great amount of material, in spite of numerous observations of the occurrence of the disease in different regions and under varying conditions, the etiology of leukemia is still very nearly as obscure as ever." H. S.

PSYCHOSURGERY. By WALTER FREEMAN, M.D., PH.D., F.A.C.P., and JAMES W. WATTS, B.S., M.D., F.A.C.S. Pp. 337; 81 illustrations. Springfield, Ill.: Charles C Thomas, 1942. Price, $6.00.

THIS is the only monograph in English upon the value of surgery in the treatment of certain types of mental disease. The history of the develop-

ment of psychosurgery is outlined from the early efforts of Burchhardt and Puusepp to the more important and impressive results obtained by Moniz. The first bits of clinical evidence of the effect of injury to the frontal lobes upon personality, such as the crow-bar skull, are carefully considered. Based upon these facts as well as upon the carefully studied cases of deliberate bifrontal lobectomy for the removal of brain tumors, a case is made for section of the prefrontal association pathways in the treatment of certain types of mental disease. Eighty carefully studied cases form the basis of this monograph. The preoperative care, the operative technique and postoperative sequelæ are carefully considered. Especially interesting is the description given of the patients' reactions in the operating room as the last of the four frontal quadrants is sectioned.

In the selection of cases for this procedure the best results were obtained in the involutional depressions and the obsessive tension states. The schizophrenics were less frequently benefited. Three operative deaths occurred in this series.

Whether or not the use of surgery in the treatment of mental disease has any appeal, this book should be thoroughly studied. The cases are described clearly and in detail. The facts are presented impersonally and without bias. There is a noticeable lack of special pleading or an effort to suggest that any panacea has been found. The authors simply detail certain facts about a relatively new—and, to many psychiatrists—radical treatment of mental disease.

But they do more than simply this. A definite step forward has been made in unraveling the psychophysiology of the frontal lobes. Whether or not the conclusions drawn on these points are correct, it must be admitted that, looked at solely as a bit of pure research and regardless of any benefit to the patients, important facts with regard to the functions of the frontal lobe have been discovered.

The format of the book is excellent; the print clear; the illustrations more than adequate. Every psychiatrist should read it if only for the purpose of developing arguments against the use of surgery in mental disease.

F. G.

PAIN. BY SIR THOMAS LEWIS, M.D., F.R.S., Physician in Charge of Department of Clinical Research, University College Hospital, London; Fellow of University College, London. Pp. 192; 27 figures. New York: The Macmillan Company, 1942. Price, $3.00.

THIS monograph is a review of the author's experimental work on pain, correlated with pertinent experiments of other investigators. Thus a well-rounded picture is obtained of the present status of the subject up to the time when the author's work was interrupted by war. The early chapters furnish the anatomic background, stating in detail which parts of the body may give rise to pain and which may not. The quality of pain is then analyzed. It appears that the popular concept of pain as being pricking, stinging, burning, etc., is ill-founded; that the quality of pain depends not on the stimulus but on the tissue and that from the standpoint of pain there are only two kinds of tissues, the superficial and the deep.

Superficial tissues comprise the skin and certain mucous membranes; deep tissues are what the term implies, and in addition, the glans penis and nasal mucosa. Corresponding to the two types of tissue we have two types of pain and two only, which are qualitatively different. These may be exemplified by pricking the skin (superficial pain) and by squeezing the finger web (deep pain).

The factors concerned in the pain of inflamed skin are discussed, though in less detail than the Reviewer would have wished. Head's division of

sensation into protopathic and epicritic is found not to be supported by more recent observations, and to be no longer useful as a hypothesis.

The latter part of the book is concerned largely with referred pain, which is a subject too large for summary in this review. I will merely state the author's opinion on how impulses arising from viscera, *e. g.*, the heart, are referred to the distribution of somatic nerves of the same segment. Such reference, he believed, is due not to diffusion of impulses through the gray matter of the spinal cord, as postulated by Sturge, but rather take place in the sensorium. The viscera are represented in the sensorium only in mass and not in detail. Impulses received from such areas are referred by the sensorium to regions well represented in detail, that is, the somatic regions. The present work deals with pain in general rather than with pain of individual organs. And the general reader may be warned that this is not an easy book to read and comprehend. M. M.

MEDICAL MANUAL OF CHEMICAL WARFARE. [Anonymous.] Reprinted by permission of The Controller of His Britannic Majesty's Stationery Office. Pp. 121; 10 plates, several tables. Revised Edition. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1942. Price, $2.50.

THIS manual, prepared by the British for the use of medical officers in wartime, and now reprinted in the United States, gives in concise form descriptions of the various gases used in warfare, the effects that they produce, and the methods to be used in treatment.

Gases are divided, as usual, into Vesicants, Lethal, Harassing and Accidental varieties. Of the vesicants, in fact of all the gases, Mustard Gas is still regarded as the most important and is given corresponding space. Its systemic effects are understated, however, and as usual, its toxic effect on the bone marrow has been overlooked.

The illustrations have been reproduced so badly that they would much better have been omitted. Considering the size and price of the book, one might have expected a much better job, though it is still a useful, practical compend. E. K.

NEPHRITIS. By LEOPOLD LICHTWITZ, M.D., Chief of the Medical Division of the Montefiore Hospital; Clinical Professor of Medicine, Columbia University. Pp. 344; 120 illustrations. New York: Grune & Stratton, Inc., 1942. Price, $5.50.

THERE is perhaps no branch of medicine in which our knowledge is increasing as rapidly as in Bright's disease. A new monograph on this subject is scarcely justified unless it presents the results of modern work fully and clearly. This the present work does not do. For example, the mechanisms of albuminuria and hypertension are explained neither fully nor clearly from the modern viewpoint. The author appears to dislike the clearance tests. Probably the most valuable part of the book is 25 case reports in tabular form showing the effects on volume and specific gravity of the urine and on blood chemistry produced by administration successively of water, 750 cc. NaCl, 10 gm., and urea, 20 gm. The subjects covered are glomerulonephritis and nephrosis, but not nephrosclerosis. M. M.

ANNUAL REVIEW OF PHYSIOLOGY. By JAMES MURRAY LUCK, Editor, Stanford University, Volume IV, 709 pages. Stanford University, Calif.: American Physiological Society and Annual Reviews, Inc., 1942. Price, $5.00.

THE purpose, nature, character, and scope of the Annual Review of Physiology is now well known. The reviews of the subjects presented in

this volume maintain the high standard set in previous years. The subjects and authors of the reviews are as follows: Permeability—Blinks; Physiological Effects of Neutron Rays—Aebersold and Lawrence; Physiological Aspects of Genetics—Strandskov; Developmental Physiology—Hamilton and Willier; Water Metabolism—Peters; Growth—Avery; Energy Metabolism—Chambers, Shorr and Barker; Physiology of the Skin—Baird, Lever, and Spies; Peripheral Circulation—Hertzman; Heart—Visscher; Blood—Smith; Digestive System—Van Lieve; Kidney—Shannon; Electrophysiology—Gerard; Spinal Cord and Reflex Action—Ruch; Central Nervous System—Hines; Autonomic Nervous System—Hare and Hinsey; Sense Organs—Hartline; Metabolic Functions of Endocrine Glands—Long; Physiology of Reproduction—Hisaw and Astwood; Physiological Psychology—Richter; Applied Physiology—Behnke and Stephenson; Pharmacology of Drug Addiction—Smith. S. G.

THE RETINA. The Anatomy and the Histology of the Retina in Man, Ape and Monkey, including the Consideration of Visual Functions, the History of Physiological Optics, and the Histological Laboratory Technique. By S. L. POLYAK, M.D. Pp. 607; 100 illustrations (1 in color). A fiftieth anniversary publication of the University of Chicago Press, Chicago, 1941. Price, $10.00.

IMPORTANT information on the retina, scattered in journals, books and even in ancient manuscripts, has been diligently collected and presented by the author in a one volume monograph. In addition, he includes the results of his own investigations on the retina and supplements his historical and morphologic survey with a discussion on the physiologic problem of this complex organ. A large number of figures and an up-to-date bibliography make the book complete. The reader will be greatly satisfied, having in his hands a book written by a scholar who is master of his subject. This monograph is one of the most valuable contributions of recent years in the field of medical literature. G. DER.

EDITH CAVELL. By HELEN JUDSON. Pp. 288; frontispiece of Edith Cavell. New York: The Macmillan Company, 1941. Price, $2.50.

THE story of Edith Cavell, a supreme example of the German inability to comprehend the reactions of enemy minds, regains the poignant interest that it held over the emotions of those engaged in the first World War. The author, who was able to interview Miss Cavell's friends and relatives, visit the scenes of her activities and study her unpublished letters and the complete German dossier of the trial, gives a satisfying picture of this unique life of devotion to humanity, as such, culminating in her final famous remark to the Rev. Mr. Gahan in prison: "Patriotism is not enough; I must have no hatred nor bitterness to anyone." It was in this sense that when Nationalism was rampant Shars classed her as "heretic" and it was this in turn that led the author to explain and set forth Miss Cavell's true personality.

Those medically minded will find a further interest in the effect of heredity on her puritanical sense of duty combined with kindliness and practical help to the unfortunate, and in her achievement in raising the nursing profession in Belgium to new standards and efficiencies.

Though one may disagree with the author as to the illegality of the execution according to the German code (was she guilty of "conducting soldiers (mannschaften) to the enemy,") the reasons offered for selecting for execution the only English subject and one Belgian out of all those convicted seem cogent. For different reasons, this nurse stands with Florence Nightingale as the chief glories of the nursing profession. E. K.

NUTRITIONAL DEFICIENCIES. DIAGNOSIS AND TREATMENT. By JOHN B. YOUMANS, A.B., M.S., M.D., Association Professor of Medicine and Director of Post-Graduate Instruction, Vanderbilt University Medical School, Nashville; assisted by E. WHITE PATTON, M.D. Pp. 385; 14 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $5.00.

THE announced purpose of this volume is to glean from the great mass of the literature the information most helpful to the practising physicians to "a proper understanding and management of the nutritional deficiencies . . . ." The vitaminoses naturally occupy the greater part of the book, but deficiencies of iron, iodine and protein are also included, together with brief mention of the rôle of the "trace" metals, kind of the essential fatty acids in nutrition.

An appendix contains the factual material summarized in tabular form, tables indicating the "excellent" and the "good" sources of the food factors, and detailed descriptions of accepted methods for diagnosing each deficiency (*e. g.*, the use of the Cowgill chart or the Williams and Spies formula for determining the adequacy of the vitamin intake). A useful index is included. E. W.

ESSENTIALS OF PATHOLOGY. By LAWRENCE W. SMITH, M.D., Professor of Pathology, Temple University School of Medicine, and EDWIN S. GAULT, M.D., Associate Professor of Pathology, Temple University School of Medicine. Foreword by JAMES EWING, M.D., of the Memorial Hospital, New York City. Second Edition. Pp. 960; 685 illustrations, 140 plates, many in color. New York: D. Appleton-Century Company, Inc., 1942. Price, $10.00.

PURSUING their original ideal of a practical, concise, up-to-date text which eliminates confusing details and imprints vividly upon the minds of medical students only the fundamental facts of pathology, the authors have retained the illustrative and repetitive feature of case histories and abundant pictorial material, sacrificing minutiæ for brevity. The section on the fundamental pathologic processes has been enlarged and amplified to include pathologic physiology and some modern theories, the case histories have been shortened, and a bibliography has been added. As in the first edition, emphasis is placed upon such currently important problems as neoplasms, parasitic infestations, and oral and respiratory diseases, with perhaps too little on such older favorites as syphilis, and central nervous system tumors.

Supplemented by complete lectures and demonstrations, the volume should be adequate, perhaps ideal, for basic reading, but cannot be used as a reference handbook. M. F.

THE PATHOLOGY OF TRAUMA. By ALAN RICHARDS MORITZ, M.D., Professor of Legal Medicine, Harvard Medical School; Lecturer in Legal Medicine, Tufts College Medical School; Pathologist, Massachusetts State Dept. of Public Safety. Pp. 386; 117 illustrations. Philadelphia: Lea & Febiger, 1942. Price, $6.00.

THE first part of this book deals with general considerations of the relation of trauma to infection, trauma and tumors, types of injurious agents, and general tissue reactions to injury. Then the gross and microscopic pathology of each organ is dealt with separately. In addition to anatomic changes, many functional disorders are discussed, such as shock, neurogenic disturbances of the cardiovascular system, post-traumatic

neurogenic disturbances of the bladder, sequence of functional changes in asphyxia.

There are descriptions of the changes resulting from detonations of explosives, but the emphasis is not upon the effects of modern warfare but rather upon the traumatic injuries encountered by any pathologist, with quite detailed information useful in medicolegal cases of violent deaths and settlements for compensation for accidents.

The book is full of interesting and unusual observations, accurate details, and has many excellent photographs. The author writes critically and expresses sound judgment, and an unbiased point of view when presenting controversial matters. I. Z.

NEW BOOKS

Edinburgh Post-Graduate Lectures in Medicine. Vol. 2 (1940-41). Pp. 540; several figures. London, Eng.: Oliver & Body, 1942. Price, 12/6 net.

Pulmonary Tuberculosis and Its Treatment. By HANS JACOB USTVEDT, M.D. (OSLO), First Assistant Physician to the State Hospital, Oslo; Formerly First Assistant Physician to the Ullevaal Municipal Hospital, Oslo. Translated by A. L. JACOBS, M.R.C.P. With a Foreword by W. D. W. BROOKS, D.M. (OXON), F.R.C.P. Pp. 252; 45 figures. London, Eng.: John Bale & Staples, Ltd., 1942. Price, 25/-.

The Modern Treatment of Venereal Diseases. By E. T. BURKE, D.S.P., M.B., CH.B. (GLAS.), Lieut.-Col. (late) Royal Army Medical Corps; Formerly Director of the London County Council (Whitechapel) Clinic; Consul and Venereologist in the Public Health Department of the London County Council; Lecturer in Venereal Diseases in the London Hospital Medical College, Univ. of London; Member of the Sub-Committee on Antisyphilitic Remedies of the Therapeutic Trials Committee, Medical Research Council; Assistant Editor, "British Journal of Venereal Diseases." Pp. 105, many tables. London, Eng.: John Bale & Staples, Ltd., 1942. Price, 12/6d.

Synopsis of Pathology. By W. A. D. ANDERSON, M.A., M.D., Assistant Professor of Pathology, St. Louis University School of Medicine; Pathologist, St. Mary's Group of Hospitals. Pp. 661; 294 illustrations, 17 color plates. St. Louis, C. V. Mosby Company, 1942. Price, $6.00.

This volume is intended to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks and reference works. By the presentation of pathology in a compact and condensed form, it is designed to be useful to the medical student, to the dental student studying general pathology, and to the clinician who must maintain familiarity with the foundation sciences of medical practice . . . . The objectives of the volume preclude bibliographic reference to many authors whose works have been consulted, although indebtedness to them is acknowledged. The references which have been included were chosen because they are reviews, or refer to subjects in which there has been recent interest or advance in knowledge. This volume partakes of many merits and limitations of works of its kind. E. K.

Microbiology and Man. By JORGEN BIRKELAND, PH.D., Assistant Professor in Bacteriology, Ohio State University. Pp. 478; 35 figures. Baltimore: Williams & Wilkins Company, 1942. Price, $4.00.

The Pleuro-subpleural Zone. By J. SKLADAL, Reader in General and Experimental Pathology, Caroline University, Prague; Head of the Chest Department, Bulovka Hospital, of the City of Prague; Consulting Physician, the Masary, Institute for Treatment of Lupus, Prague-Motol. Pp. 103; 11 plates. Cambridge: The University Press; New York: The Macmillan Company, 1942. Price, $275k.

Fluorine and Mental Health. Edited by FOREST RAY MOULTON. Publication of the American Association for the Advancement of Science, No. 19. Smithsonian Institute Bldg., Washington, D. C. Publication Committee, H. TRENDLEY DEAN, PAUL C. KITCHIN. Pp. 101; many figures and charts. 1942. Price, $3.00.

NEW EDITIONS

National Formulary. Prepared by the Committee on National Formulary by authority of the American Pharmaceutical Association. Official from November 1, 1942. Seventh Edition. Pp. 690. Washington, D. C.: American Pharmaceutical Association, 1942. Price, $6.00.

Conforming with the new practice of the U. S. Pharmacopœia, this revision has been made 5 instead of 10 years after the previous one and becomes official on Nov. 1, 1942. Although it is still primarily a book for the pharmaceutical rather than the medical profession, N.F. VII contains a new chapter on ingredients of reagents and preparations for use in the clinical laboratory, including a summary of the chemical and physical properties of the various substances involved, which should make the book distinctly useful to workers in clinical laboratories. As compared with N.F. VI, this edition contains 97 new items, 71 of which were official in the last (XI) revision of the U.S. Pharmacopœia but are not included in the forthcoming XII revision; in this list are such things as vinegar of Squill, Cantharis, Creosote, Dichloramine T, Guaiacol, Iodoform, Kino, Dover's Powder, Santonin, Syrup of Ferrous Iodid, Tincture of Ferric Chloride, Tincture of Veratrum Viride, and Trional. Thus is retained the traditional status of the N.F. as an official repository for drug preparations that are declining in popularity but are still rather widely used. C. S.

Stedman's Practical Medical Dictionary. By STANLEY THOMAS GARBER, B.S., M.D., University of Cincinnati, College of Medicine. Fifteenth Edition, revised, with Etymologic and Orthographic Rules. Pp. 1257. Baltimore: Williams & Wilkins Company, 1942. Price, with Thumb Index, $7.50; without index, $7.00.

This new edition, after 3 years, the first to appear under the sole authorship of the late Dr. Stedman's nephew, worthily maintains the high standard and tradition of its predecessors. This edition has been completely reset, has 45 fewer pages than the 13th edition and is slightly smaller. The changed type is less pleasant to the eye, but probably saves searching time. As one would expect, hundreds of new titles are included and many that have become obsolete have been omitted. The latest variations in bacterial terminology (see Bergey's Manual, 1939) have been included, so that one should now master 500 new species, new genera, families and even a new order—"Canlobacterioles," as well as new names for old acquaintances. Fortunately, chemical synthetics are not offered in the same detail! E. K.

The Care of the Aged (Geriatrics). By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, U. S. Public Health Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I.; Special Consultant, Rhode Island Department of Public Health. Fourth Edition. Pp. 589; 50 illustrations. St. Louis, C. V. Mosby Company, 1942. Price, $7.00.

Gray's Anatomy. By HENRY GRAY, F.R.S.; Late Fellow of the Royal College of Surgeons; Lecturer on Anatomy at St. George's Hospital Medical School, London. Edited by WARREN H. LEWIS, B.S., M.D., Member, the Wistar Institute of Anatomy and Biology, Philadelphia. Twenty-fourth Edition. Pp. 1428; 1258 figures, mostly in colors. Philadelphia: Lea & Febiger, 1942. Price, $12.00.

Starling's Principles of Human Physiology. Edited and Revised by C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. (BIRMINGHAM), Jodrell Professor of Physiology in University College, London. Chapters on the Special Senses Revised by H. HARTRIDGE, M.A., M.D., Sc.D., F.R.S.; Professor of Physiology at St. Bartholomew's Medical College. Eighth Edition. Pp. 1257; 673 figures. Philadelphia: Lea & Febiger, 1942. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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THE TREATMENT OF MÉNIÈRE'S SYNDROME

It was early in the course of our own Civil War, in 1861, to be exact, that Ménière[8a] described a group of symptoms which he thought constituted a separate disease entity. His description of the symptomatology of the disease which bears his name is a classic, and little has been added through the years. Ménière's syndrome is common, affects people in the middle years of life, and shows a characteristic triad of symptoms: vertigo, tinnitus and deafness. The etiology is unknown; its pathology is still a subject for investigation and some degree of speculation. The treatment of Ménière's syndrome remains a varied one.

At the present time the most effective treatment of Ménière's syndrome may be divided into two categories: medical and surgical. According to Grove,[7] surgical intervention should be reserved for those patients who have not responded to a medical régime, to those patients who for economic or other reasons cannot be kept on a medical régime, and for those patients whose occupations are such as to preclude the possibility of any return of the vertigo because of carelessness in following a medical régime. Of the surgical measures proposed, it seems to Grove that total section of the acoustic nerve is indicated for those whose hearing in the affected ear has fallen below a usable level and that the differential section of the vestibular portion of the nerve is the operation of choice for those with usable hearing. These operations should not prove hazardous in the hands of the competent neurosurgeon. Dandy[5] maintains that Ménière's syndrome can be permanently cured by division of the auditory nerve. The procedure carries almost no risk to life. When there is reason to save remaining hearing, partial division of the nerve is done. The vestibular branch can be

divided, leaving a part of the auditory branch intact. Generally, three-fourths of the anterior part of the auditory nerve is sectioned to insure total elimination of the vestibular fibers. Division of three-fourths of the auditory branch of the nerve does not affect hearing, apparently because of redundant fibers carrying similar functions. If there is a division of one auditory nerve, or only its vestibular portion, no permanent loss of vestibular function ensues. Immediately following operation the patient may or may not have transient attacks of dizziness not unlike an attack of Ménière's syndrome. Gradually, however, it decreases and then disappears. Only occasionally will it persist for a long period of time. Tinnitus, too, may or may not disappear following section of the nerve; if it persists it may or may not improve, but in about 50% of cases it disappears completely. Section of the entire eighth nerve or its vestibular portion usually eliminates the violent attacks of vertigo, but that it does not always do so is indicated by Walsh and Adson[14] who state that of 20 patients who had a section of either the whole nerve or its vestibular portion, 15 were able to resume their work, and of the remaining 5, 3 were highly nervous women. They suggest that in those cases which do not gain relief from the total nerve section the condition is bilateral and the opposite vestibular nerve should be sectioned, but in the majority of cases the vertigo, if not completely eliminated, is improved to the extent that the individuals can resume their occupations. Mollison[9] exposes the prominence of the external semicircular canal by a simple mastoid operation and injects a few drops of absolute alcohol into the membranous canal after removal of its bony covering. He reports that 74% of patients operated upon considered themselves cured, 10% as not benefited, and 16% lost track of. Berggren[3] employs the same method of alcohol injection but through another approach. He makes a flap of the entire posterior one-half of the membrana tympani, turns it upward and forward, and after scarifying the mucous membrane over the promontory he perforates the bone in this region with a dental burr. Putnam[12] suggests drilling into the superior canal with a burr through a subtemporal approach and then destroying the labyrinth by coagulation.

As a result of their experiments, observations and therapeutic results, Mygind and Dederding[11] conclude that in Ménière's syndrome there is a disturbance of water metabolism not only in the ear but also, with individually varying location, in greater or smaller parts of the entire organism. These disturbances have a tendency to periodic fluctuation caused by a series of external and internal factors which seem to exert their action essentially through a partly local, partly general, vasomotor—especially capillariomotor—dysfunction. In the past their treatment consisted of a restricted fluid intake of about 700 cc. daily and sometimes even as low as 350 to 400 cc., a diet low in salt for the purpose of increasing diuresis, a reduction diet for patients who were overweight, together with exercise, massage and light therapy to stimulate vasomotor tone. Furstenberg, Lashmet and Lathrop[6] disagree with the deductions of Mygind and Dederding, namely that water retention is the cause of the Ménière syndrome and when the body accumulates water that sodium is also stored, and direct their treatment to a reduction of the body sodium. They maintain that

the retention of water and sodium will produce an attack; but loss of water and sodium does not produce an attack. The retention of water without sodium will not produce an attack, while the loss of water with a retention of sodium will produce an attack. Furstenberg therefore places his patients on a salt-free diet to limit the intake of sodium, and on ammonium chloride to encourage an increased excretion of sodium while permitting the patients all the water desired. He states that the water intake need not be considered if the concentration of the sodium ion in the body is kept at a low level. Brown[4] and Bartels[2] have reported favorable results with this régime. Walsh and Adson[14] report a series of 186 cases of which 152 were treated with a low salt diet with or without the addition of medication for salt elimination. They employed potassium nitrate instead of ammonium chloride and found it to be as efficacious. Of the 152 patients treated with a low salt diet with or without the addition of sodium-eliminating medication they found 34% experienced complete relief of the vertigo, 28% experienced variable degrees of improvement, and 38% experienced no relief whatever. Morsch[10] treated 4 patients with Ménière's syndrome who also had symptoms of avitaminosis for vitamins A and C. He reports an improvement in the vertigo, tinnitus and deafness after intensive vitamin treatment.

In 1940 Shelden and Horton[13] advocated the use of histamine in all cases of Ménière's syndrome without exception and claimed immediately satisfactory results in a large proportion of cases. They reject the views which place pathologic changes in Ménière's syndrome in various cerebral structures and believe that the lesion is situated in the inner ear, that it consists essentially of localized alteration in permeability of the capillary wall and that this causes regional edema. The labyrinth is held to be the specific site most frequently involved, and tinnitus and diminution of hearing is considered evidence of secondary cochlear involvement. Four of 15 patients were treated by the subcutaneous route and 11 intravenously. The patients in the latter group were given intravenously from 1 to 3 doses of 1.9 mg. histamine acid phosphate dissolved in 250 cc. normal physiologic salt solution. The time for each administration was approximately 1½ hours. Spectacular results were reported in all 15 patients, and no ill-effects were noted following the use of histamine. For the prevention of future attacks, Horton finds that an adequate maintenance dose is usually 0.1 to 0.2 mg. histamine given subcutaneously 2 to 4 times a week. In commenting on the work of Shelden and Horton, Woltman[15] states that because of its value and ready applicability he does not believe that the treatment proposed by Furstenberg will be supplanted by the histamine treatment, but that the latter is of great value when vertigo and vomiting are extreme.

To Atkinson[1] it seems not unjust to conclude from the evidence he has found that histamine is not suitable for universal application in cases of Ménière's syndrome. It is suitable for selected cases only, and only by assigning individual cases to their correct group can effective treatment be assured. It is on a par with typing pneumonia cases for serum treatment. Confusion has crept in—his mail is ample evidence of it and the precipitating cause for his paper—because histamine has two effects, an immediate and a remote, and the two have not been

distinguished. The immediate effect is vasodilator, in consequence of which it often gives immediate and sometimes dramatic relief from a vasoconstrictor attack, though no more immediate or dramatic than other peripheral vasodilators. Its remote effect, by inducing a resistance to its action in the body in the same way in which a vaccine produces a resistance to the effects of a microörganism, is *nil* or actually even vasoconstrictor. For this reason its repeated administration, while exceedingly effective in the vasodilator group as a desensitizing agent, in vasoconstrictor cases not only fails, after the initial doses, to produce the desired effect but sometimes even makes matters worse. Histamine will not relieve all, or even most, cases of Ménière's syndrome. Preliminary accurate grouping is essential to success.

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DERMATOLOGY AND SYPHILOLOGY

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PHOTODYNAMIC EFFECTS IN DERMATOLOGY

PART II

THIS paper is a continuation of a review in the previous volume (*Am. J. Med. Sci.*, **203**, 608, 1942) on Photodynamic Effects in Dermatology, in which we propose to discuss the diseases with a prominent cutaneous aspect in which photodynamic effects appear to play a leading part. Because of the voluminous material, the discussion will be limited to diseases in humans, and only some of the more important diseases will be discussed in detail. In addition, some mention will be made of prevention and treatment of the local cutaneous reaction to light.

The effects of light on the abnormal or morbidly reacting skin of human beings has been known for about 150 years. Rasch[155] has sum-

marized the important contributions dealing with the development of knowledge concerning the diseases of the skin which are caused, in part, at least, by light. The first to describe one of the diseases produced by the sun was Willan,[206] in 1798. He called the condition eczema solare, but Rasch believes Willan's disease to be similar to the eczema-like polymorphic light eruption later described by himself.

In 1835 Rayer[156] described a patient with vesicular and papular lesions on the hands and back produced by light, and in 1860 Bazin[9] described hydroa vacciniforme. Kaposi[99] (1870) described xeroderma pigmentosum but was not aware of the relationship of this disease to light (Unna,[191] 1894). Other conditions were subsequently described: J. Hutchinson[89] (1878), prurigo æstivalis; Veiel[200] (1887), eczema solare. In 1906 and 1907 Dubreuilh[41c] stated that most of the epitheliomata of the face and so-called senile alterations of the skin were produced by the light's rays.

As is the case even today, confusion has marked the clinical differentiation of these various dermatoses. The early attempts to classify them were largely clinical and the only evidence that light was a causative factor was the fact that the eruptions were limited to the exposed parts, and that the patient gave a history of exposure to sunlight just before the attack. Rarely was there an attempt to reproduce the lesions by exposure. Further stimulation to study of these diseases was the discovery of porphyrin by McCall Anderson[3] (1898) in the urine of 2 patients with hydroa. Subsequent demonstration of photodynamic action and a possible allergic mechanism to explain abnormal sensitivity to light have been discussed in the first part of this review.

That animals have diseases due to photosensitivity has likewise been known for over 150 years and the various diseases have stimulated considerable research. The reader is referred for complete discussions of the photodynamic diseases in animals to Mathews[125a,b,c] and Blum.[19a,b]

Blum[19a,b] has formulated simple requirements comparable to the laws of Koch in microörganismal diseases, before a given condition may be attributed with certainty to photodynamic action:

1. The symptoms of light sensitivity must be elicited by exposure of the animals to sunlight, preferably to sunlight through window glass.
2. A photodynamic substance must be isolated in pure form, which will produce the symptoms if injected into the experimental animals only when followed by exposure to light.
3. It must be demonstrated that the wave-lengths which produce the sensitivity in postulates (1) and (2) are identical. The study of the absorption spectrum of the photosensitizing substance isolated in the development of postulate (2) should be of assistance in establishing postulate (3), since the action spectrum for the production of the symptoms of photosensitivity should resemble the absorption spectrum of the substance.

These requirements are not necessarily fulfilled in all diseases usually attributed to light, but nevertheless they offer a guide for future study. While they were apparently proposed for diseases in animals, they apply with equal force to man.

Numerous classifications of diseases, either produced or affected by light, have been proposed. Blum's[19b] attempt to develop a simple general classification is a step in the right direction, particularly from the experimental standpoint. His classification is as follows:

A. Skin lesions produced only by radiation which induces the sunburn of normal skin (wave-lengths shorter than 3300 Å). (Polymorphic light eruption; skin cancer; xeroderma pigmentosum.)
B. Skin lesions due to abnormal photosensitizing substances in the skin. (Urticaria solare.)

We have adopted that of Hausmann and Haxthausen[75] (1929), not because it is necessarily the most exact, but because it is clinical. The Hausmann and Haxthausen classification is as follows:

I. The action of light on pathologically light-sensitive skin.
  A. Hydroa æstivale.
    1. Hydroa æstivale with congenital porphyrinuria.
    2. Hydroa æstivale with chronic porphyrinuria.
    3. Hydroa æstivale without porphyrinuria.
  B. Chronic polymorphic light eruption.
  C. Pellagra.
  D. So-called pellagroid eruption due to light.
  E. Unclassified eruptions due to light, accompanying metabolic and other internal disturbance.
  F. Sensitization of the skin to light by medicaments.
    1. Exogenous.
    2. Endogenous.
  G. Xeroderma pigmentosum.
  H. Late xeroderma pigmentosum, Seemanshaut, other photogenic forms of skin cancer.
  I. Degeneration of elastic and collagen tissues of the skin.
  J. Photoelectric dermatitis.
II. Skin diseases exacerbated or precipitated by light.
  A. Action of light on acute exanthemic infections.
    1. Variola.
    2. Other acute exanthemata.
  B. Intrinsic skin diseases.
    1. Acne vulgaris.
    2. Eczema.
    3. Multiform exudative erythema.
    4. Lupus erythematosis.
    5. Pityriasis streptogenes faciei.
    6. Psoriasis.
    7. Rosacea.
    8. Toxic exanthemata.
    9. Urticaria.
    10. Other skin diseases.

Many review studies have appeared from time to time dealing with the various dermatoses produced by light. Among them are those of Rasch,[155] Greenbaum,[68a] Anderson and Ayres,[2] Bechet,[11a] Mercer,[128] S. Epstein,[48] Hübner,[85] Lampe,[112] and especially the monograph of Blum.[19a] Special studies devoted to individual phases of this problem will be mentioned in appropriate places.

Hydroa Vacciniforme seu Æstivale. Since Bazin[9] (1860) first described hydroa vacciniforme there have been several designations for this disease or variations of it, leading to much confusion. Rasch[155] believed that the name *hydroa vacciniforme* had been applied to two different diseases, that described by Bazin, the typical form resulting in cicatrix; and the other, consisting of a special symptom complex composed of porphyrinuria, the outbreak of large pemphigus-like blebs on the face, ears, and hands, which lead to gangrene and a great loss of substance, and was first attributed to the action of light by McCall Anderson.[3] Prurigo æstivale is also confused with hydroa vacciniforme. Epstein[48] has shown that Pick's[147] differential criteria for prurigo

æstivale are all subject to exception, making the absolute differential diagnosis impossible. In addition, the occurrence of porphyrinuria and mutilating dermatoses of the exposed parts have led a number of authorities to discuss the porphyrias as part of the same picture. Because hydroa is not associated with all cases of chronic or congenital porphyria and because porphyrinuria does not occur in many of the cases of hydroa, we are discussing the two subjects separately.

Clinically, hydroa vacciniforme seu æstivale consists of an eruption of variously sized bullæ appearing early in life, gradually subsiding after puberty, usually distributed on the exposed parts. In the majority of the cases scarring occurs with resultant severe disfigurement of the nose, ears and fingers. In certain abortive cases, scarring may be absent. In others the scarring may be so extensive as to resemble scleroderma. Hypertrichosis, hyperpigmentation, and excessive sensitivity to trauma (epidermolysis bullosa[190]) may be present. Porphyrinuria may be associated with the cutaneous lesions and occasionally alterations in the liver and spleen may also be noted.[193] Keratitis has also been observed. The teeth may be discolored by porphyrin. In some cases there may be an hereditary factor.

As in many phases of the problem of light-sensitive dermatoses, Blum and his associates[19a,21,23] have been instrumental in furthering our understanding of hydroa vacciniforme. Because of the occurrence of porphyrinuria in certain cases of hydroa vacciniforme it was felt that this substance might be the photosensitizing agent involved in the production of such lesions. If hydroa lesions are the result of such action, they should be reproduced by the same wave-lengths as those to which porphyrins sensitize the skin. If porphyrin really were the sensitizing substance, Blum and Pace[23] thought it should be "possible to produce the lesions of hydroa by subjecting the skin to any wave-lengths between the lower limit of sunlight (about 2900 Å) and about 6500 Å, provided the intensity and time of exposure were great enough; but the greatest sensitivity should lie between about 3000 Å and 4500 Å." Blum and his associates, in common with many other investigators attempted to reproduce the lesions experimentally. The results of these studies were varied and inconclusive. They failed to demonstrate that the lesions of this disease are produced by the wave-lengths to which porphyrins sensitize the skin. They also found that repeated exposure to radiations which elicit sunburn in normal skin failed to reproduce the hydroa lesions.

Porphyrias. There is a group of congenital disturbances of unknown etiology characterized by a disturbed metabolism of the pyrrols and associated with the excretion of large amounts of porphyrins. Porphyria is to be distinguished from porphyrinuria, which refers merely to the excretion of abnormally great amounts of prophyrins in the urine. Günther[71] classified the various clinical subgroups in this concept as modified by Waldenström,[201] into congenital, acute, and chronic types.

Recent contributors to the study of these conditions are Mathews,[125a] Turner and Obermayer,[190] Turner,[189a] Dobriner and Rhoads,[37] Schwartz and Watson,[171] Nesbitt and Watkins,[136] and Hoagland.[83] Most of these studies are fully documented and bring the subject thoroughly up to date.

Congenital porphyria is attended with great sensitivity to light and the excretion of large amounts of Type I porphyrins. This type of porphyria was recently reviewed by Turner and Obermayer[190] who discussed 86 cases,9 of which were considered doubtful. Dobriner and Rhoads[37] summarized the clinical manifestations as "(1) The excretion of large amounts of porphyrin; (2) discoloration of the teeth and bones by impregnation with uroporphyrin I; (3) sensitivity of the skin to light in the spring and summer, a symptom which often appears first in childhood. Blistering of the exposed areas of the face and extremities is observed, and the lesions heal with scar formation followed in many cases by deformity of the affected tissue." Turner and Obermayer point out, however, that hydroa vacciniforme is not the only dermatosis associated with porphyria, since approximately 14 cases of epidermolysis bullosa and other dermatoses have been less rarely reported in this connection. In some instances porphyrins have also been absent. Turner and Obermayer cited other less common concomitant findings in their review, including lesions in the eyes, the thyroid, the liver, the spleen, and the blood (anemia). Schreus and Carrié[170] record that porphyrin was found in the blister fluid. The urine in congenital porphyria is usually burgundy red with a brown tinge (varies from pale pink to almost black) and contains large amounts of coproporphyrin Type I and uroporphyrin Type I. The feces may contain an abnormally large amount of coproporphyrin.

Turner and Obermayer were unable to reproduce experimentally the eruption typical of porphyria in their patient, but note that their failure was one of a long series. They hypothesize that "in view of the existence of hydroa, epidermolysis bullosa and porphyria as independent clinical entities, and in consideration of the familial occurrence of each, it is suggested that each is a genetically different disease. The frequent coëxistence of porphyria and a cutaneous disease may depend on some spatial or chemical relationships of the genes determining these conditions."

Acute Porphyria. Acute porphyria has been studied especially recently by Mason, Courville and Ziskind,[123] Waldenström,[201] Dobriner and Rhoads,[37] Turner,[189a] Schwartz and Watson,[171] Nesbitt and Watkins,[136] and Hoagland.[83] Acute porphyria has been subdivided into toxic and idiopathic varieties, but Nesbitt and Watkins[136] believe that both types probably represent the same condition. Clinically, acute porphyria is characterized chiefly by gastro-intestinal disturbances and central nervous system involvement. While there may be spotted pigmentation, the skin is little affected, and the patients rarely show light sensitivity, but do excrete large amounts of uroporphyrin Type III, especially during the acute phase. It is a familial disease, probably inherited as a dominant Mendelian characteristic. Turner states that the acute manifestations are relieved by intravenous calcium therapy.

Chronic Porphyria. This type of porphyria occurs in patients whose condition cannot be classified either as congenital or acute and is characterized by an increased excretion of porphyrins (coproporphyrin Types I and III; uroporphyrin Types I and III in various reported cases.[37] Patients with this type of porphyria are somewhat sensitive to light, responding with hydroa-like lesions.

Chronic Polymorphic Light Eruptions. Although various dermatological pioneers ascribed cutaneous affections of an eczematous character to light,[200,206] it remained for Rasch in 1900[155] to group a number of these eczematous dermatoses under the heading of "eczema-like polymorphic light-eruption," which his pupil Haxthausen[76] subsequently clarified. Rasch included in his concept a "rash, which causes intense itching, consists partly of oval and round, slightly raised, erythematous spots of variable size, partly of irregular grouped vesicles and partly of small scab-covered papules. On the hands, which are diffusely swollen and cyanotic, there are found numerous infiltrated, or urticarial, erythematous plaques and remnants of pustules with a small central dimpled scab." He believed that one should group all light-induced eruptions of a papular, erythematous lichenoid and urticarial type under the collective term, "chronic polymorphic light dermatitis." Haxthausen classified under this concept Hutchinson's summer prurigo, eczema solare, prurigo æstivale and summer acne. Rasch believed that certain skins reacted to the same stimulus with different manifestations but Urbach and Konrad[195] have seen patients with alternation of lesion types in different attacks.

The literature on this subject has become extensive and much of it consists of case reports. Among the chief recent contributions are those of Rasch,[155] Urbach and Konrad,[195] Turner,[189b] S. Epstein,[48] and Blum.[19a]

Blum[19a] has, we believe, collated convincing data to show that there is a sound reason for collecting these cases into one group. He states that most of the patients respond abnormally to the sunburn spectrum. A few of them, however, react abnormally to other wave-lengths. Urbach and Konrad[195] found their patients sensitive to wave-lengths between 4900 and 7000 AU. Templeton and Lunsford[186] found 1 of their 2 patients sensitive to sunlight but not to wave-lengths longer than 3340 ÅU. Shaumann and Lindholm's[168] patient was sensitive, according to Blum, to the sunburn spectrum. These authors in 1938 demonstrated absence of sensitivity to visible radiation. Turner[189b] felt that the sun "causes the prurigous eruption by acting on a 'primary reacting substance' whose absorption spectrum shows a sharp rise and fall between 3020 Å and 3125 Å."

The mechanism underlying the production of this type of light-sensitive dermatosis is unknown. There are some[48,91,95] who maintain from their experience that allergy plays an important rôle, and the definite reports of passive transfer of the sensitization[295,51] point to this conclusion. Turner[189b] stated definitely, on the other hand, that this is not a condition properly described as "physical allergy." Mühlman and Akobjan[135] rendered rats sensitive to the mercury arc irradiation by injecting blood serum from a patient with prurigo æstivale. Rasch thought there was an hereditary factor in some of the cases. Jausion and his co-workers[91,95] have attempted to demonstrate a bacterial origin for polymorphic light eruptions and recommended gold therapy. Riccioni[157] suggested an endocrine factor in the cause. Porphyrinuria has been demonstrated in some of the patients, but no evidence has been produced to prove that the eruptions are due to a photosensitizing substance.

Photosensitivity in Pellagra. The connection between sunlight and the dermatitis of pellagra was first noted according to various reviewers[72,73,125a,177] by a number of authorities about 1771 to 1794.[1,38,56,183] In 1792 Gheradini[61] produced skin lesions and other signs and symptoms of pellagra in 10 pellagrins by exposure to the sun's rays. In 1794 Strambio[183] produced skin lesions repeatedly on various parts of the body by exposure of pellagrins to the sun. Since these historic beginnings the influence of the sun's rays on the lesions of pellagra has been a subject of debate. Smith and Ruffin's[177] admirable summary of this relationship states:

> Casal noted a seasonal variation in the incidence of pellagra, with a peak which corresponded to the spring equinox. In Italy one of the common names applied to this disease by the peasants is *mal del sole* (disease of the sun), while certain Italian physicians have described the lesions as due to "sunstroke of the skin." Many modern clinicians have stated their conviction that there is a close relationship between exposure to sunlight and the development of cutaneous lesions in a pellagrin. Various observers have produced typical cutaneous lesions in a pellagrin by exposing normal or recently healed areas of skin to direct sunlight. Gherardini demonstrated the effect of the sun by systematically uncovering various parts of the body of each patient. Bouchard, Hameau and Ormsby had their subjects wear fenestrated gloves; Wilson had them expose both arms, and we have produced typical lesions in subjects by having each expose one arm to direct sunlight. Randolph prescribed a sun bath for a Negro with pellagra. After a short period of exposure the patient complained of intense burning of the skin, and he was promptly removed to a dark room; nevertheless, severe dermatitis appeared and was followed by stomatitis, diarrhea and dementia. The patient finally recovered.
>
> The presence of lesions on unexpected portions of the body, such as the elbows, knees, sacrum, scrotum and perineum, has led certain students of pellagra to deny the influence of sunlight in the production of the dermatitis. Tucker, Enright and Goldberger and Sebrell recognized that an existing lesion can be accentuated by exposure to sunlight, while Spies stated that the cutaneous lesions heal equally well regardless of whether the patient is kept in the dark or exposed to direct sunlight. Bigland and Spies failed to produce lesions in pellagrins by exposing them to sunlight, and Gougerot, Burnier and Meyer, Crutchfield, Bassi and Spies reported that they noted no unfavorable response to ultraviolet radiation.

From their own studies on 35 pellagrins, Smith and Ruffin found that a moderate exposure to the direct rays of sunlight resulted not only in dermatitis but in an exacerbation of the constitutional symptoms of the disease in 13 of the patients. In 2 other patients this exposure produced the constitutional symptoms, but no dermatitis. Balbi[8] tried to determine the relationship between sunlight and pellagra by utilizing the observation of Jobling and Arnold,[97] that improvement occurred when pellagrins were kept in a dark room. He hospitalized 7 patients in the dark for 8 to 10 days and noted the cutaneous lesions daily. The diet was controlled and no special treatment was given. The patients were permitted to leave their rooms in the evening. All the patients were improved.

Efforts to produce pellagra lesions due to light in lower animals likewise have yielded inconclusive results. Mathews[125c] who reviewed the experimental studies came to the conclusion that it is possible that the ill-effects of a corn ration and exposure to light may represent the combined action of malnutrition and heat rather than photodynamic sensitization.

The interesting finding by Jobling and Arnold[97] of an aspergillus from the digestive tracts of pellagrins, which produced a fluorescent substance on artificial media, has not been confirmed. The authors considered these results to be of etiologic importance in pellagra, since the fluorescent substance proved to be photodynamic on injection into rats. Mathews[125a] considers such results of little value because the fluorescent substance was not administered through the digestive tract.

The association of light sensitivity with increased porphyrin excretion has stimulated much interest in the problem of porphyrin metabolism in pellagra. As early as 1932 increased porphyrinuria was noted in endemic pellagrins in Italy.[124] This observation was apparently confirmed by others, particularly by Beckh, Ellinger and Spies.[12] Recent studies have thrown considerable uncertainty on the rôle of these porphyrins in causing the dermatitis of pellagra. Furthermore, the increased excretion of porphyrins has been found particularly in alcoholic pellagra, as well as simple alcoholism; and since excretion of coproporphyrin III occurs in intoxications associated with damage to the liver, a malfunction of the liver sufficient to interfere with normal handling of the porphyrins is thought to occur in pellagra (Rosenblum and Jolliffe[162]).

Another factor involved in pellagra and porphyrin metabolism is the relationship of nicotinic acid to pigment excretion. This subject has been thoroughly covered by the review of Elvehjam:[46]

> Beckh, Ellinger and Spies (1937) reported an increase in the amount of coproporphyrin 1 or 3 in the urine of pellagrins and a decrease following the treatment of the pellagra with yeast or liver extract. Later Spies, Gross and Sasaki (1938) found that nicotinic acid also produces a decrease of porphyrinuria in pellagrins. They also found that the porphyrinuria associated with other diseases promptly decreased following nicotinic acid therapy. Watson (1938) found that the urinary coproporphyrin in alcoholic pellagrins was not correlated with the Beckh-Ellinger-Spies test. In a later paper Watson (1939) concludes that the color reaction observed in the urine during pellagra is due to urosein. It occurs as a chromogen which changes to a pink or red pigment upon addition of hydrochloric acid to the urine. Another pigment soluble in chloroform may also be present which appears to be indirubin. Both of these pigments may be noted in the urine of patients not having clinical pellagra and therefore further work is necessary in order to relate the appearance of pigments directly to nicotinic acid deficiency. Meiklejohn and Kark (1939) have also found substances in the urine of pellagrins capable of giving the urosein reaction. They were unable to find any unusual amount of coproporphyrin in four samples of urine supplied by Dr. Spies and suggest that it would be more proper to refer to the Beckh-Ellinger-Spies test as indicating the presence of pigments capable of producing the urosein reaction.

Experiments carried out by Kühnau[108] in which mice were given injections of photodyn, one group of the animals being given injections of nicotinic acid amide at the same time, and all the animals exposed to the sun's rays for 15 minutes, indicated that the injurious effect of photodyn was not neutralized by nicotinic acid amide, but on the contrary the mice which received both injections died sooner than those which did not. When the nicotinic acid amide was given within 10 minutes after the photodyn, and the animals exposed to the sun $\frac{1}{2}$ hour later, some differences were noted in the behavior of the two groups. Although the animals treated with nicotinic acid amide did not survive, the course of the sun injury was milder, and death occurred later than in the untreated group. Kühnau[108] concluded that nicotinic

acid amide is apparently an indispensable factor in the protection of the normal skin against ray injuries, but that no unequivocal relationship can be established between this vitamin and porphyrin metabolism.

Urticaria Solaris. Urticarial wheals are rarely produced by exposure to sunlight. Many of the text-books and studies on dermatology scarcely mention urticaria due to light.[84,192a]. Pillsbury and Sternberg[149] in their discussion on papular urticaria stated that sunlight has been considered by several investigators as a cause of this condition, and while they were not prepared to dismiss light as a factor, they did not believe it to be the principal cause. The question of light urticaria has recently, however, become the subject of much interest. Extensive studies have been published by Blum,[19a] Blum, Allington and West,[20] Blum and West,[24] Epstein,[48] Arnold,[5] and Rajka.[154]

The definition of urticaria solaris as given by Blum[19a] identifies it with the triple response (Lewis) produced by blue and violet light. S. Epstein classifies this condition among the allergic light dermatoses. The first case reported was that of Merklen[129] (1904). Among the other authentic cases reported were those of Ward,[202] Ochs,[137] Duke,[43] Frei,[57] Beinhauer,[14] Vallery-Radot[198,199] and his co-workers, Wucherpfennig,[208] Weiss,[203] Blum and co-workers,[20,24] Epstein,[48] Arnold,[5] and Rajka.[154]

In solar urticaria exposure of the skin to sunlight for brief periods is followed within a few minutes by the appearance of erythema limited precisely to the exposed area. The erythema is replaced shortly by edema, limited to the irradiated area and as the edema develops, a flare occurs in the surrounding unexposed skin. The amount of sunlight needed to produce the response is small, and the reaction is independent of the patient's health, age, and sex. Many attempts have been made to determine the portions of the spectrum which are responsible for the urticarial lesions. Ward[202] and Ochs[137] found that "violet light" produced urticaria in their patients. Duke[43] found that his patient probably was affected by the spectral regions from about 3200 to 5000 ÅU and the far-red and infra-red. Beinhauer's[14] patient was sensitive to the ultraviolet portion of the spectrum. Frei thought that the short visible and long ultraviolet radiations (3200 to 6000 ÅU) were operative in his case. Vallery-Radot[198,199] and his co-workers found the effective wave-lengths to extend throughout the visible spectrum, ultraviolet and infra-red radiations being ineffective (4000 to 5000 and 4000 to 7000 ÅU). Wucherpfennig's[208] patients showed greatest sensitivity to the long ultraviolet, but also to other light rays which darken photographic plates. Epstein[48] found wave-lengths of 4000 to 4500 ÅU as well as ultraviolet radiation probably, to be effective. Blum and West,[24] in their careful study, determined that the spectral region effective in eliciting wheals was between 3900 and 5200 ÅU. Arnold[5] found his patient's sensitivity to lie in the portion of the spectrum from 3800 to about 5000 ÅU. Rajka[154] determined that his patient's urticaria was produced by rays between 4000 and 5000 ÅU, and occasionally by wave-length 4359 ÅU lying in the blue spectrum and abundantly emitted by the mercury arc.

In their study of the various factors involved in the production of urticaria solaris, Blum and his co-workers[19a,20,24] found that temperature had little effect on the threshold time, but had great effect on the latent period which precedes the appearance of erythema. They found

that the photosensitivity of different parts of the body varies widely. The abdomen and the lumbar region are more than 20 times as sensitive as the face and hands. In addition, they noted that there may be a local decrease in photosensitivity, without affecting the reaction of the rest of the body. They presumed that the sensitizing substance was a carotinoid, since the absorption spectrum of carotenoids lies almost entirely within the blue and violet band.

Duke[43] was the first to call attention to physical agents as the cause of urticaria, and he, as well as other authors, have collected evidence to demonstrate allergy in their cases. Others, however, have failed to produce satisfactory proof that the conditions in their cases were based on allergy.[194] This same difference of opinion has extended to the question of the allergic or non-allergic nature of light urticaria, as well as of other dermatoses with a light sensitization factor. (See Part I, Blum and Epstein, sulfanilamide.) Blum[19a] has decried the "allergic," viz. idiosyncratic, nature of urticaria solaris. On the other hand, Jausion and Pagès,[94] Epstein,[48] and more recently Rajka[154] have been strong advocates of the "photoallergic" concept. Some of the reported cases give a personal or familial history of allergy, and passive transfer in light urticaria has been accomplished.[154] Bernstein[18] reported passive transfer to guinea-pigs. In Rajka's[154] case there was whealing, accompanied in addition to the passive transfer, by hemoclastic crisis and general symptoms. Rajka succeeded in partial desensitization.

There is a distinction between urticaria solaris and the urticarial reaction occurring after local injection of photodynamic substances followed by radiation. In the latter case the whealing results in pigmentation which is a sequel to epidermal injury. No pigmentation follows spontaneous urticaria, and the wheals resulting from histamine injection.[20] This is considered by Epstein to favor the allergic nature of urticaria solaris.

Photodermatitis. Photosensitization by Substances Coming in Contact with the Skin; Berlock Dermatitis; Dermatitis from Vegetable and Other Substances (Fig Dermatitis; Dermatitis Bullosa Striata Pratensis [Meadow Grass Dermatitis]).

For about 25 years dermatologists have shown an increasing interest in photodermatitis induced by the local application on the skin of certain plant substances and subsequent exposure to sunlight. The noxæ were thought to be an aromatic oil or some oleoresinous portion of the plant to which the cutaneous surface was exposed. Freund described the most common of this variety of photodermatitis, Berlock dermatitis,[163] which follows the application of certain toilet waters and perfumes and subsequent exposure to sunlight. The first case of Berlock dermatitis observed in this country was reported by Gross and Robinson.[69] In 1926 Oppenheim[139a,b,140a,b,c] described meadow grass dermatitis (*dermatitis bullosa striata pratensis*), and eruption occurring in persons taking sunbaths who were at the same time in contact with certain meadow plants. Kitchevatz[104a,b,c,d,e] since 1934 published a series of studies on a photocatalytic dermatitis due to contact with figs. The literature on this whole subject has become extensive. Some of the more important contributions in recent years are: (*a*) Berlock dermatitis, Gross and Robinson;[69] Greenbaum;[68b] Rogin and Sheard;[161] Goodman.[64a,b] (*b*) Meadow grass dermatitis, Corson;[32] Robinson.[158]

(*c*) Fig dermatitis, Kitchevatz;[104d,e] Behcet, Ottenstein, Lion and Dessauer.[13] (*d*) Various plants, Kuske;[109a,b,c] O'Donovan.[138] (*e*) Parsnip, Hirschberger and Fuchs;[82] Jensen and Hansen.[96] (*f*) Lime oil, Sams.[166]

The excellent papers by Oppenheim,[139b] S. Epstein,[48] Sams,[166] and the chapter in Blum's book[19a] are complete reviews of this subject and deserve careful study.

The various photodermatitides are considered in one place because, while their clinical manifestations are somewhat varied, fundamentally their modes of production are relatively similar. The photodynamic effects of externally applied hydrocarbons will be discussed in connection with cutaneous cancer. In Part I of this review,[180a] it was stated that Guillaume[70] showed that a photosensitizer must reach the Malphigian layer of the epidermis in order to produce observable effects, and no photodynamic responses occur unless the layer is exposed, by abrasion or otherwise, to the action of the substance. Accordingly, photodermatoses are not regularly produced by external contact because most substances do not penetrate below the corneous layer. There are, however, photosensitizing substances which do penetrate below the corneum and effect photosensitization.

Berlock Dermatitis. This peculiar pigmentation resulting from the successive action of application of toilet water and exposure of the skin to sunlight or to artificial ultraviolet irradiation, is usually found on the neck and chest, and appears as dark red spots, changing to brown, slightly mottled with red. The shape of such discoloration simulates a small drop of flowing fluid. Berlock dermatitis generally appears during the summer.

The exact pathogenesis of this dermatosis is unknown. It is believed that one is dealing with a personal susceptibility or with various factors such as climate, perspiration, brand of perfume or some contaminant of the perfume, and short intervals between the application of the perfume and exposure to sunlight. Most of the evidence favors a personal predisposing factor (Gross and Robinson,[69] Greenbaum,[68b] Wise and Sulzberger,[207] Rogin and Sheard[161]). The photosensitizing substance is likewise undetermined, but the process may be reproduced in susceptible individuals by the local use of bergamot or citron oil followed by irradiation (Freund,[58] Del Vivo[36]).

Some investigators believe impurities, copper (Goodman[64b]) or chlorophyll,[161] in oil of bergamot may be the inciting factor. On the other hand, the application of bergamot oil without trauma, *i. e.*, friction, does not produce any reaction without exposure to light. According to Del Vivo[26] bergamot oil sensitizes the skin to blue and violet light.

Photodermatitis of Vegetable Origin. Since Oppenheim first described dermatitis following sunbathing in meadows and fields, studies have appeared either describing new plants as sources of such trouble, and presenting data to indicate the possible mechanism or wave-lengths involved.[96,104,166] Cases have been reported from many lands: Germany, France, Russia, Denmark, Italy, Spain, Switzerland, Austria, all other European countries and the United States.[32,139b,158]

Meadow Grass Dermatitis.—This process has recently assumed a military importance as was suggested by Hirschberger and Fuchs[82] and Englehardt.[47] The former noted lesions in soldiers who had used green plants, including parsnip, in camouflage. Englehardt[47] found that 45 of

120 soldiers, drilling on a meadow near a beach, developed a vesicular dermatitis a few hours later. Blum advisably points out that the lesions of meadow grass dermatitis may cause confusion because they resemble those produced by mustard gas. The sharp circumscription of the lesions and the resulting persistent pigmentation of meadow plant dermatitis tend to differentiate it from the plant dermatitis of the primrose type, and point to a photodynamic origin.[35,47] (See Gorodinsky,[65] whose patient had an experimentally reproducible linear bullous dermatitis from *Dictamnus fraxinella caucasicus* without the use of sunlight.)

Patients with meadow grass dermatitis give a history that they developed pruritic bullæ in more or less striated arrangement, appearing the day after the sunbath. The process clears readily, but leaves pigmentation which may persist for months. It is not produced at seashores or other places where sunbaths are taken, if there is no opportunity for contact with plants. Kuske[109a,b,c] describes the chief clinical characteristics of exogenous percutaneous photosensitivity from plants as being (1) latent period, on an average of 7 to 12 hours; (2) the acme which depends on the intensity of irradiation and manifests itself as edematous swelling ranging to bulla formation; and (3) residuum, of long-continued pigmentation.

The exact cause of meadow grass dermatitis is unknown. Oppenheim originally thought it was due to an animal parasite (Milben) but later[140] he leaned toward a plant or plant product as the source of the dermatosis.[26,54,60,121,145,176] Philadelphy intimated that sunlight might play a rôle in the cause of the eruption but Kitchevatz[104c] made the first extensive experimental studies. He showed that the red rays of the spectrum acting through an intermediate catalytic substance, chlorophyll, rendered the skin more sensitive. The photosensitization occurs only where chlorophyll is placed in intimate contact with the cells of the skin. Acid increases the action and the sensitivity cannot be passively transferred. Kitchevatz's explanation for this process is not accepted by many.[13,82,92,93,96,139a,140] Hirschberger and Fuchs[82] in studies with parsnip plants (*Pastinaca sativa*) thought that the active agent was flavone. Oppenheim[139b] believed that sensitivity to etherial oils in plants was the basis for the dermatosis. Cummer and Dexter[35] asserted that the active substance was an aromatic oil but could not prove this experimentally with extracts of the gas plant applied to the skin. Kuske[109a,b,c] in a series of detailed studies employing juices from 5 plants concluded that phytogenous photosensitization was due to the presence of similar sensitizers, furocumarines. He showed that the furocumarines sensitize human skin for ultraviolet long waves, especially in the spectral field around 3340 and 3660 ÅU. Jensen and Hansen[96] studied the active spectral range for dermatoses produced by the parsnip plant, and found the wave-lengths which produce the lesions to lie in the ultraviolet longer than 3200 to 3600 ÅU. Blum[19a] calls attention to the fact this spectral region does not correspond to the absorption spectrum of chlorophyll nor with the sunburn spectrum. Sams[166] presented a study of 11 patients suffering from photodermatitis due to oil from the Persian lime (*Citrus aurantifolia var. Swingle*). He was able to reproduce the photodynamic reaction experimentally and showed that the concentration of the photodynamic agent, the length of time of exposure,

the subject, the location of the application, and previous radiation determined the intensity of the subsequent dermatitis. The longer wavelengths of ultraviolet radiation (3100 to 3700 ÅU) are involved in the production of the dermatitis and subsequent pigmentation. The chemical nature of the photocatalytic agent is still undetermined.

Sunlight and Cancer of the Skin. It has been repeatedly contended since 1894 (Unna[191]) that prolonged exposure to the sun may stimulate the production of malignant tumors. Blum[19c] has collected and critically analyzed this entire subject. His study and the résumé in his book[19a] are the chief sources of this discussion. Other recent studies of the relationship of cancer to irradiation are those of Körbler,[107] Büngeler,[28] Roffo and Luchetta,[160] Poth,[150] Rusch and Baumann,[164] Rusch, Kline and Baumann,[165] Doniach,[39] Teutschlaender,[187] Whitmore,[205] Grady, Blum and Kirby-Smith,[67] Blum, Kirby-Smith and Grady,[22] Hueper,[86] Apperly.[4]

Since the description of "Seaman's skin" by Unna[191] as a precancerous condition attributed to continued exposure to light, some authorities[15,40,41a,b,90,114,132,146,160,175] have emphasized the rôle of sunlight among the factors causative of cancer while others have opposed this view.

The evidence for the rôle of sunlight in the production of skin cancer has been entirely clinical, *i. e.*, it has consisted of attempts to correlate clinical findings with intensity of exposure and susceptibility to sunlight. Roffo,[159a,b–g] especially convinced of the importance of the influence of the sun, based his opinion on three principal arguments: (1) malignancy of human skin appears most frequently on those parts of the body most exposed to light; (2) malignancy of the skin may be produced in laboratory animals by prolonged exposure to light; and (3) there is an apparent direct relationship between cholesterol content, exposure to light, and the incidence of malignancy. In addition, Blum[19c] has deduced from the literature that those in favor of sunlight as a carcinogenic agent state that cancer of the skin is more prevalent in outdoor workers and that the incidence is higher in regions of the earth which receive greater insolation and it occurs more frequently in blondes than brunettes. Blum believes that the clinical facts cited in support of these claims are still open to question, but that within recent years support has come to the theory of direct causation of cancer by sunlight from experiments on laboratory animals. These studies not only demonstrate that cancer can be caused by sunlight, but offer opportunity to study the various factors involved.

Artificial production of cancer in animals was first accomplished by Findlay[49] in mice. His work was followed by similar studies independently conceived and prosecuted.[19c,79,152,159a,b–g] More recently similar successful experiments were made by Huldschinsky,[87] Beard, Boggess and von Haam,[10] Rusch and Baumann,[164] and Rusch, Kline and Baumann.[165] Roffo[159d,e] showed that natural sunlight, as well as mercury arc radiation, may cause tumors in rats. The tumor lesions were chiefly confined to bald or sparsely hairy parts of the animals (eyes, ears, paws or parts shaved for experimental purposes). The tumors were either epitheliomas or sarcomas, and were transferable to normal rats.[159f] The active wave-lengths were found to be in the region of the sunburn spectrum. Rusch, Kline and Baumann[165] found the carcinogenic wave-lengths to be between 2900 and 3341 ÅU. Very little

radiant energy was needed to initiate the changes which culminate in tumor formation. The length of the precancerous period varied inversely with the daily dose of radiant energy. The minimum time for the development of tumors appeared to be about $2\frac{1}{2}$ months. It was not necessary to irradiate the animals throughout the precancerous period; once initiated, carcinogenesis proceeded without further exposure to radiant energy and in isolated cases several months elapsed between the end of radiation and the appearance of tumors. Grady, Blum and Kirby-Smith[67] found by a specially controlled method of exposure of mice to mercury arc radiation that a 100% incidence of tumors may be induced on the ears of "male strain A" mice by such radiation. At higher dosages of radiation, the time of appearance of the tumor is little affected by the dosage, but at lower dosages this time increases markedly with decreasing dosage. They also showed that the production of tumors depends upon the quantity of radiant energy applied rather than upon the intensity of the radiation. The tumors thus produced were chiefly fibrosarcoma, less frequently combinations of fibrosarcoma and squamous cell carcinoma and rarely squamous cell carcinoma alone.[67]

The type and quantity of radiation (sunburn radiation) are not the only factors involved. So far only rats and mice have been shown to be definitely susceptible to tumor production, although suggestive results have been obtained in other animals. The color of the animal is important, since Rusch and Baumann[164] found that considerably more radiation was required for tumor production in C 37 brown mice than for strain A and strain C albino mice. They also found that black mice developed a smaller percentage of tumors than albinos and that the time required was greater. The color of the hair may have served as a filter in the case of the colored mice. Rusch, Baumann and Kline[165] found that the rate of tumor production with ultraviolet light could be altered by the local application of certain substances to the tissues developing tumors. Mineral oil accelerated tumor development most rapidly. Cholesterol in oil caused acceleration, other substances and oils were less stimulative and linseed oil retarded tumor formation. Baumann and Rusch[164] found that the rate of tumor development varied with different diets. Lesions were produced more rapidly on a high fat diet, while brain extract or liver retarded tumor production. Addition of 2% cholesterol to the stock diet did not affect the rate of tumor production, although a marked increase in liver fat and cholesterol resulted. These results suggested that the rôle of cholesterol in tumor production was a limited one in contrast with those of Roffo who claimed that (*a*) the cholesterol content of tumors and precancerous lesions is higher than that of normal tissue; (*b*) tumors may be induced in man and animals with light alone as a carcinogenic agent; (*c*) the cholesterol content of the skin exposed to light is higher than that of skin protected from light. Bergmann[16] denied the importance of the belief that cholesterol is changed into a carcinogenic agent in the skin by irradiation. In summary, Blum[19c] asserts that "while the idea that sterols in the skin may be changed to carcinogens by the action of ultraviolet light is an attractive one, it must be admitted there is little evidence in its favor at present." The same applies to Körbler's[107] suggestion that porphyrins might be photosensitizing agents for cutaneous tumor production.

In connection with human cancer and sunlight, there are a number of factors of importance. Among them are: geographic distribution of sunlight; distribution of cutaneous cancer and its relationship to sunlight; the character of the skin; season, sex, menstruation (irregular increase in sensitivity), pregnancy (sensitivity increases after the third month), and advancing age (decreases) (Ellinger[45]).

Lawrence[114] discussed the low humidity and abundant sunshine as a causal factor for cancer of the skin in Australia. The moisture in the atmosphere impedes the passage of ultraviolet rays. He found that rodent ulcer is over 20 times as frequent in dermatologic practice in Australia as in England. Molesworth[132] and Duhig[42] confirm Lawrence's opinion. Duhig[42] found that 25% of hospital admissions for cancer at Brisbane are cases of skin cancer. The same state prevails in our own arid Southwest.[178] The incidence of skin cancer is 3 to 4 times as great in Atlanta, Georgia as in the northern city of Chicago, Illinois.[134] Peller, Stephenson and Souder[141,142,143] have recently reviewed the incidence of cancer of the lip and skin in the United States Army and Navy and found that such cancer occurs more frequently among soldiers and sailors born and who presumably resided in their early years in southern states than among those born in northern states.

Blum critically reviews the claims that skin cancer is more prevalent at regions of the earth that receive greater insolation and points out that "seldom are these supported by statistics of cancer incidence, and there do not exist sufficient data of cancer on the intensity of the tumor-producing wave-lengths incident at different regions of the earth to permit a real correlation. The distribution of total sunlight can be estimated with some accuracy but this is much more difficult for the wave-lengths that produce tumors."

Apperly[4a] has made an interesting study of the relationship between solar radiation and cancer mortality in North America, in which he points out that several observers have noted that the incidence of cancer of the various organs among peoples of European origin varies considerably with geographic location, although the total cancer death rate shows comparatively minor variations. Furthermore, Peller in a small series of cases showed that environments and occupations in which skin cancer is more prevalent, other cancers are relatively less prevalent. Others have noted the converse—that cancer of the skin does not protect against visceral cancer. The total cancer mortalities of various American states and Canadian provinces are shown to fall with increasing solar radiation and with the number of people exposed thereto, and are independent of the production of skin cancer. Apperly[4] from his statistics concludes that we may be able to reduce our cancer deaths by inducing a complete or partial immunity by exposure of suitable skin areas to sunlight or the proper artificial light rays of intensity and duration insufficient to produce actual skin cancer. In another study, Apperly[4b] found that when mortality rates of pernicious anemia and skin cancer (corrected for other causes than exposure to sunlight) are correlated, it appears that the incidence of pernicious anemia is closely related inversely to effective solar radiation.

Distribution of Cutaneous Cancer and Its Relation to Sunlight. Most skin cancers appear on the human face, one of the most exposed areas of the body. Furthermore, certain areas of the face are more frequently the sites of cancer than others (regions about nose and

eyes[19c]). Aside from the possible action of sunlight,[41,110] other factors may be involved in the localization of cutaneous cancer to the face: (1) basal cell cancer occurs along embryonic lines of closure of facial skin;[62,119,126] (2) cancers that develop around the nose and eyes developed from embryonic rests; (3) shading of certain areas by anatomic (chin shades neck) or artificial (caps and hats) coverings; (4) certain factors preventing absorption of effective wave-lengths. Thickness of the epidermis, particularly the corneum, on different parts of the face might be of importance in determining the location in skin cancer if sunlight is an important etiologic factor; (5) certain dermatoses (lupus erythematosus) have similar distribution; (6) exposed parts are affected by minor traumata.

The Character of the Skin and Cancer. The relationship of the skin color to light sensitivity has been discussed in the first part of this review. With specific reference to skin cancer, Taussig and Williams[185] stated that it is more common in blondes than in brunettes. Hyde[90] commented on the result of cutaneous cancer in Negroes. This has been reaffirmed by many others.[77,111,132,144,159,167]

Occupation and Cutaneous Cancer. It is difficult to ascertain whether occupations subjecting persons to greater exposure to sunlight are predisposing to cancer. There are statements pro and con; by equally competent observers.[86,119,142,209] The occupation may present other factors than sunlight to account for cancer occurring in the face. For example, the handling of tar preparations[28,39,187,209] which produces a cancer limited largely to the exposed parts (but compare scrotum).

The pathogenesis of the production of cutaneous cancer by sunlight is not definitely determined. There are many hypotheses to explain the process and certain important data have been collected from animal study. However, more exact information, clinical and experimental, is needed for the solution of this problem.

Xeroderma Pigmentosum. Xeroderma pigmentosum is a rare cutaneous affection which appears early in life and terminates in malignancy, so that persons affected with it usually die by their 15th year. These individuals may show successively or simultaneously erythema, pigmentation, atrophy or tumor formation. Photophobia may be a prominent symptom. Xeroderma pigmentosum is an inherited abnormality, and Cockayne[31] has shown that it is a recessive character due to a single gene and it is not sex-linked. It occurs frequently in the product of consanguinous parentage.

Kaposi[99] who first described xeroderma pigmentosum failed to note its frequent onset after solar exposure.[133] The first to suggest this relationship was Unna[191] (1894) but subsequent investigators had various experiences from attempts to demonstrate abnormal reactions to light. The results of these studies are summarized in the publications of Lynch,[118] Mathews,[125a] King and Hamilton,[102] and Blum.[19a] Blum concludes that these studies leave open the possibility that sunburn radiation precipitates the lesions of xeroderma pigmentosum. It seems most probable "that the abnormal response is the result of some abnormality of the skin which is exacerbated by the action of the sunburn radiation, but that the condition might develop independently of this radiation although its appearance may be accelerated by it" (Blum[19a]). Lynch[118] found that the sensitivity was to wave-lengths

2800 to 3100 ÅU. Zoon[210] found an increased sensitivity to the long wave-length sunburn spectrum (around 3000 ÅU).

Pigmentation Due to Photosensitization. The normal pigmentary response of the skin to sunlight is not considered here. There are, however, a number of circumstances of widely different character leading to hyperpigmentation, in which light plays a prominent rôle. Other pigmentary dermatoses provoked by light and externally applied sensitizers (Berlock dermatitis, meadow grass dermatitis) have been discussed.

In 1913 Lewin[115] noted that workers employed in the manufacture of electrical cables involving coal-tar and petroleum products were sensitive to light. Similar observations were made by Kistiakowski,[103] Mierzecki[130] (petroleum products), and Foerster and Schwartz.[53] Fleischhauer[53] showed that only coal-tar products are photosensitizing while wood tars are not. Foerster and Schwartz[53] examined more than 500 men in 4 factories; more than half of them had either melanosis or cutaneous lesions, chiefly dermatitis. The condition was confined to handlers of pitch or of pitch products, but those most intimately in contact with pitch were affected the least, while those who had the most severe dermatitis and the most intense pigmentation were outdoor workers. Indoor work, necessitating direct contact with pitch and pitch vapor and exposure to high temperatures, did not appear to be definitely associated with development of dermatitis. But when an indoor worker was placed at yard work, an inflammation of the face invariably followed. This disappeared, although the pigmentation persisted, when he returned to indoor work.

The dermatitis was characterized by diffuse erythema and desquamation at times associated with severe edema; it involved chiefly the face and neck particularly the nasolabial areas and chin, and was frequently accompanied by conjunctivitis and occasionally with labial herpes and cheilitis. The pigmentation was diffuse and intense, considerably darker than ordinary suntan, and it was confined to those surfaces exposed to sunlight. Pitch comedones and folliculitis on the face, neck, hands and forearms were commonly observed, and keratoses and papillomas were found occasionally. Only 2 epitheliomas were seen, and these apparently were not due to pitch or tar. While some men were affected more severely than others, apparently none sufficiently exposed were immune. Tolerance with persistent pigmentation was developed in some cases, but most of the men had to be rotated among various jobs, and some were so hypersensitive that they could not be employed in the daytime but worked satisfactorily on night shifts. Pigmentation was not permanent, but it persisted at least for several months after removal of the worker from exposure.

Similar dermatoses (melanosis of Riehl) were frequent during the last war, in Germany, according to Habermann,[72] and were attributed to the use of impure products and adulterants because of the blockade of the Central Powers by the Allies, but since there were many cases in other countries not under blockade, Thibierge[188] suggested that blockade was not the chief factor. Others intimated that it might have come from contact with tar or oil. Recent studies from South America[148,151] suggest that this process in Argentina is the result of application of cosmetics containing photosensitizing substances, the skin reaction

being provoked by sunlight. Dietary and endocrinologic factors, however, may still play a part in the production of this pigmentary state.

In 1930 Fleischhauer[52] found that Lianthal, a coal-tar product, sensitized the skin to light (sunlight even through window glass or light from a quartz lamp) although, if it were applied in the usual manner and allowed to dry, it acted as a light protective. On the other hand, wiping the excess off after about 15 minutes, the skin was found to be light-sensitive. This photosensitization lasted for as long as 72 hours after the application. This observation (photochemical change in crude coal tar (?)[80] is the basis for the Goeckerman treatment for psoriasis in which the patient is irradiated after having been treated with a tar preparation.[63]

The action spectrum for lesions produced by light after application of tar was found to be between 3300 and 5000 ÅU by Fleischhauer[52] while Foerster and Schwartz[53] found the range in their cases to be between 3900 and 5000 ÅU.

Other cutaneous pigmentations produced through the action of light are those caused by heavy metals: silver (argyria);[81] arsenic (arsphenamine dermatitis); gold;[30,169] mercurochrome;[153] and a transient discoloration of the nails due to mercury bichloride.[29a,98,184] This latter condition is not a true pigmentation since Callaway demonstrated that the solution of mercury bichloride coming in contact with the sulphur in the skin and nails and activated by light causes the formation of a black mercuric sulfide which is responsible for the discoloration.

Lupus Erythematosus. There has been a widespread impression recently that lupus erythematosus is increasing,[11a,b,106,117,180,204] but Gahan's figures[59a,b] from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital during the years 1936–1940, do not seem to substantiate such an increase, at least for the period studied. At any rate, an increasing number of investigators have been reporting the onset of some of their cases of lupus erythematosus as appearing subsequent to solar irradiation.[6,11a,b,25,34,50,66,180] Although Hausmann and Haxthausen[75] found that in Copenhagen there is a great increase in the appearance of lesions in the spring and summer, Gahan[59a,b] found no particular type of seasonal variation in the incidence of the disease in New York. In a study designed to determine the factor of actinic trauma in the causation or pathogenesis of lupus erythematosus, Gahan[59a,b] found no appreciable difference between the relative frequency of the disease in the United States (0.4%) and in any other part of the world inhabited by the white race; whatever differences there may be are not based on climatic conditions. Cummer[34] found that, according to statistics, lupus erythematosus occurs about half as frequently in the Negro as in the white race. The deep pigmentation is a protection against the sun's rays.[156] In 1938 Ludy and Corson[117] found hematoporphyrin in the urine of many of their patients with lupus erythematosus of the acute and subacute types. In these individuals the hematoporphyrin disappeared with their improvement in other respects. Ludy and Corson[117] thought that this substance could readily account for the dermal changes and might serve as a danger signal against the use of certain treatments for lupus erythematosus. They also noted the presence of lead in the skins of

their patients, and thought that it might play a rôle in the pathogenesis of lupus erythematosus.

Other Dermatoses With Light Sensitization Factors. An inspection of the detailed classification of the light-sensitization dermatoses would indicate that there are many cutaneous diseases in which light might play a rôle. Recent studies have been concerned with granuloma annulare;[27,105] varicella;[120] purpura solaris;[17] epidermolysis bullosa;[100] psoriasis;[122,173] severe actinic dermatoses (resulting from increased stercoporphyria, abnormal intestinal flora and hepatopathy);[192b] pyogenic relapse and sensitiveness to light in certain dermatoses (discussed in Part I);[181] lipoid proteinosis;[197] and lymphogranuloma venereum.[179] Sonck points out in his monograph on this subject that a definite distinction is made between the photosensitivity produced by the sulfonamides used in treatment of lymphogranuloma venereum, and that due to the disease itself. This study is recommended to those especially interested.

Treatment of Light-sensitive Dermatoses. This aspect of the discussion of light-sensitive dermatoses naturally divides itself into general and local treatment. Since the causative mechanism and factors involved in many of the diseases which light tends to induce are not always known, one cannot always get at and remove the cause. Attention to certain organic abnormalities may cure or temporarily stop light sensitivity. Attention to gastro-intestinal (hydrochloric acid), hepatic, infective disorders (vaccines, removal of foci of infections), vitamins (nicotinic acid), and endocrine treatment plus the use of specific (antisyphilitic treatment);[193] gold chloride[116] or non-specific treatment (histaminase, calcium, iron)[44] have proved of benefit in certain cases. Hurst[88] apparently cured his patient by progressive light desensitization. He exposed the back daily to ultraviolet rays, beginning with a 1-inch area for 1 minute, and gradually increasing the size of the area and the length of the exposure. Treatment of patients with dermatoses due to light by intramuscular injection of hydrolysates of a number of glands of internal secretion (testes, liver, thyroid, anterior pituitary and thymus) proved successful in 28 patients at the hands of Selisky.[172] Lancaster[113] reviewed the entire subject of estrogenic hormone therapy in sunlight eruptions of the female and found various combinations of thyroid, corpus luteum and estrogenic substance helpful in 6 cases. This estrogenic therapy was tried in only 2 males in 1 of whom it produced marked improvement and in the other, whose sensitivity to sunlight developed after a severe attack of measles, an injection of 200 international units of theelin, in water, gave temporary relief for about 2 weeks but the patient subsequently regained his normal tolerance to sunlight.

Local therapy in light-sensitive dermatoses consists of finding one or a combination of substances which will filter out the offending light rays. The ideal preparation for this purpose is one which is non-irritating, easily removable, non-staining and when applied thinly, protects the skin against the undesirable action of ultraviolet irradiation, yet does not prevent tanning. Numerous recent studies of real scientific merit have appeared from time to time, listing and stating the value of many substances including proprietary preparations.[7,78,101,127,174,182,196]

Among the various preventives proposed are: naphtholsulfonic acid,

esculin or its hemologues, lithopone, titanium compounds, menthyl salicylate, certain fluorescent compounds, amino or substituted amino, benzoic acid in mineral or peanut oil, quinine bisulphate, oak bark extract, vitamin C and cumarin in bergamot oil,[101] bergamot oil;[196] denied by Miescher;[131] salol (phenyl salicylate), resorcin.

In addition to the so-called protecting substance, its concentration or combination with other protections, there are factors which influence the effectiveness of a given formula. Sweat may in itself screen some of the active radiation. Crew and Whittle,[33] for example, showed that sweat definitely screened the skin against erythema-producing radiation so that a film 1 mm. in thickness transmits only about 27% of solar radiation effective in producing sunburn.

The base likewise plays an important rôle in the action of ointments intended for protection against sunlight. Bachem and Fantus[7] found wool-fat, yellow petrolatum and diachylon ointments to have the highest sunscreen value of the ointment bases tested and yellow petrolatum was superior to white petrolatum. In a later study Strakosch[182] found that petrolatum and lanolin afforded no protection against irradiation from an air-cooled mercury vapor quartz burner. Emulsions such as aquaphor (containing 6% of a group of esters of cholesterol in an aliphatic hydrocarbon base) or Abbott's Ninol base (containing fatty acid esters of monoethanolamine, mixed with petrolatum) were applied with evidence of a slight protective action. Quinine or tannic acid did not increase the effectiveness of petrolatum or lanolin and the same drugs had only slight protective action when added to equal parts of petrolatum and lanolin. When quinine or tannic acid were added to aquaphor or Ninol base (Abbott), a considerable degree of protection was afforded.

Bachem and Fantus[7] as a result of their laboratory and clinical studies have produced 5 finished "cuticolor" preparations which are eligible for protection against light and their value seems to be similar. Choice of a given formula depends upon the effect desired. The authors claim their combinations are superior to products commercially available. The basis of the "cuticolor" preparations (lotion, paste, tragacanth paste, ointment and creme salve) is the "cuticolor" titanium dioxide the formula for which is:

Red ferric oxide	6.0 gm.
Yellow ferric oxide	8.0 gm.
Titanium dioxide	86.0 gm.

Mix by trituration.

In addition to being efficient, Bachem and Fantus' preparations are cosmetically attractive.

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Editorial Note to Medical Authors: We wish to call the special attention of author-contributors and readers of this Journal to two of the most frequent errors that appear in our manuscripts.

The first—the misuse of "milligrams per cent"—is well covered on Page 53 of the American Medical Association's book entitled "Medical Writing": "Results of chemical determinations are frequently expressed as 'milligrams per cent' or 'grams per cent.' This means literally 'milligrams (or grams) per hundred milligrams (or grams),' which in most instances is not the information that the author wishes to convey. To insure accuracy a writer should specify the unit used, such as 'milligrams per hundred cubic centimeters' or 'milligrams per 100 gm.' If a number of values are (*sic*) given close together in a section or in a short paper, it usually is sufficient to supply 'per hundred cubic centimeters' the first time the phrase appears and to use merely 'milligrams' (not 'milligrams per cent') thereafter." We have become so weary of correcting this fault—and yet probably have overlooked it in many cases—that we are taking this means of trying to reduce it for the future. We hope that other journals, and especially the Journal of the American Medical Association with its large circulation, will also emphasize the point.

We should like to regard the word "consider" as indicating that the item is still under consideration or being meditated upon, *i.e.*, that no conclusion has been reached. This is usually the first meaning given by dictionaries for this word. We believe that, some dictionaries to the contrary notwithstanding, it is improper to use the word where a decision has been reached; in which case some such word as "think to be," or "regard as" or "believe to be" or "hold as an opinion" gives the more exact meaning.

THE EDITOR.